UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR TOBACCO PRODUCTS

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ELECTRONIC CIGARETTES AND THE PUBLIC HEALTH:
A PUBLIC WORKSHOP

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March 10, 2015
8:00 a.m.

The Marriott Inn and Conference Center
Potomac Ballroom
University of Maryland University College (UMUC)
3501 University Blvd. East
Hyattsville, MD 20783

FDA:

JEANNIE LIMPERT, M.D.
Medical Officer
Center for Tobacco Products

CAROLYN DRESLER, M.D., M.P.A.
Associate Director for Medical and Health Sciences
Workshop Moderator
Center for Tobacco Products

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Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

PUBLIC COMMENT SESSION

FAWKY ABDALLAH, Ph.D.
President, Fawky Abdallah Company, Inc.

GREGORY CONLEY
President, American Vaping Association

CHRIS WEBBER
Free to Vape

BILL GODSHALL
Founder/Executive Director, Smokefree Pennsylvania

PATRICIA I. KOVACEVIC, J.D.
Director, Regulatory Affairs, Associate General Counsel
Lorillard Tobacco Company

MARIA GOGOVA, Ph.D.
Senior Principal Scientist, Altria Client Services

EDWARD A. WOLFF
Vaping Industry Alliance

GIGI MEINECKE, D.M.D.
Academy of General Dentistry

WALTON SUMNER, M.D.
Washington University in St. Louis

SCOTT BALLIN, J.D.

JONATHAN THORNBURG, Ph.D.
Director of Exposure and Aerosol Technology
RTI International

ARIEL SAVRANSKY, M.S.
American Council on Science and Health

KELVIN CHOI, Ph.D., M.P.H.
Division of Intramural Research, NIMHD
University of Maryland

CARL V. PHILLIPS, Ph.D.
Consumer Advocates for Smoke Free Alternatives Association

MARK ANTON
President, What a Smoke

ERICA HALLER-STEVENSON, M.P.H.
National Association of County and City Health Officials

JOEL NITZKIN, M.D., M.P.H., DPA
R Street Institute

STEPHEN STOTESBURY, Ph.D.
Head of Regulatory Science
Imperial Tobacco Limited

HEALTH EFFECTS IN USERS

M. BRAD DRUMMOND, M.D., M.H.S.
Assistant Professor, Pulmonary & Critical Care Medicine
Johns Hopkins University School of Medicine

ARUNI BHATNAGAR, Ph.D.
Professor of Medicine
Director, AHA Tobacco Regulation and Addiction Center
University of Louisville

PURNIMA KUMAR, D.D.S., Ph.D.
The Ohio State University

WILLIAM C. BAILEY, M.D.
Professor of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine
University of Alabama at Birmingham

CHERYL ONCKEN, M.D., M.P.H.
Professor of Medicine and Obstetrics and Gynecology
University of Connecticut Health Center

MELISSA SUTER, Ph.D.
Department of Obstetrics and Gynecology
Baylor College of Medicine

JOSEPH R. DiFRANZA, M.D.
Department of Family Medicine and Community Health
University of Massachusetts Medical School

STEPHEN S. HECHT, Ph.D.
Tobacco Research Programs and Masonic Cancer Center
University of Minnesota

THERESA M. MICHELE, M.D.
Director, Division of Nonprescription Drug Products
Office of Drug Evaluation IV
FDA Center for Drug Evaluation and Research

CHRIS BULLEN, M.B.Ch.B., M.P.H., Ph.D.
The University of Auckland, New Zealand

HEALTH EFFECTS PANEL

WILLIAM C. BAILEY, M.D.
Professor of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine
University of Alabama at Birmingham

NEAL BENOWITZ, M.D.
University of California, San Francisco

STEPHEN S. HECHT, Ph.D.
Tobacco Research Programs and Masonic Cancer Center
University of Minnesota

CHERYL ONCKEN, M.D., M.P.H.
Professor of Medicine and Obstetrics and Gynecology
University of Connecticut Health Center

ADVERSE EXPERIENCES AND RISK ASSESSMENT

JEANNIE LIMPERT, M.D.
Medical Officer, Office of Science
FDA Center for Tobacco Products

EDMOND W. ISRAELSKI, Ph.D.
Director, Human Factors
Combination Product Development, R&D
AbbVie Inc.

JAMES P. STANSBURY, Ph.D., M.P.H.
Social Science Analyst
Division of Nonprescription Drug Products
FDA Center for Drug Evaluation and Research

M E E T I N G

(8:00 a.m.)

DR. LIMPERT: Welcome back to Day 2 of our second workshop on e-cigarettes. My name is Jeannie Limpert, and I'm from the FDA Center for Tobacco Products.

Yesterday we addressed topics related to the toxicology and addiction associated with the use of these products. This morning we will first hold a public comment session.

In order to accommodate the great interest and participation, each presenter will be limited to a 3-minute presentation. After a short break, we will move to sessions on health effects in users, the role of biomarkers in assessments of health effects, the role of e-cigarettes as a cessation aid, and adverse experiences and risk assessments.

We will have one panel discussion today after the health effects section, but we will have time for clarifying questions throughout the day. Dr. Carolyn Dresler from CTP Office of Science will again be our moderator.

Like yesterday, our agenda is full, and so presenters have been asked to keep their presentations within the time period allotted and a timer will be used in order to stay on schedule. We will have an hour break for lunch and end the day at 3:45.

Please remember to bring all personal items with you when you
leave the room.

Similar to yesterday, if you have a clarifying question or
a question for the panel, if you are here on site, please write
your question on one of the cards provided and promptly give
the card to one of our volunteers. If you are participating by
webcast, you can e-mail your questions to
workshop.ctpos@fda.hhs.gov.

The workshop is being recorded. The transcript and
webcast recordings will be posted on our website when they
become available.

I would like to remind you of a few things from yesterday.
The purpose of this workshop and this series of planned
workshops is to gather scientific information about this novel
category of tobacco products. This workshop is not intended to
inform the Agency's proposed deeming rule, and we are not
looking for advice or consensus but are interested in an open
exchange and discussion of scientific information. We request
that all workshop participants be considerate and respectful of
all other participants, the information being presented, and
the opinions expressed by others.

We request that you refrain from use of all tobacco

products, including e-cigarettes and other electronic nicotine

delivery systems, throughout the meeting. The restrooms can be

found outside this room in both directions down the hallway.

Food and beverages will be available for purchase during lunch.

It will be a deli buffet lunch and will be in the Patuxent

Room, as it was yesterday.

Please note that for any immediate inquiries, Tara Goodin

will be available this afternoon.

I would now like to turn the podium over to our moderator

for the workshop, Dr. Carolyn Dresler.

DR. DRESLER: Good morning. We're going to start off with

that public session, so can I please ask the first speaker to

come up, please? And then the next speaker, if you can please

be ready in -- there's a waiter chair there, so as you're

getting up, instead of waiting across the halls, the next

speaker can be there so we're ready to go, all right?

So our first two are not here, so -- sir. A three? Okay.

So please start, sir. Number 4.

DR. ABDALLAH: Well, I'm glad I came early, so good

morning to you all.

First, I would like to thank CTP for inviting me to give

comments on the definitions and health aspects of cigarettes

versus e-cigarettes. I here would like to explain one of the

lowest risks in my opinion. This is the law, this is not my

wording.

What is a cigarette? Any roll of tobacco wrapped in paper

or any substance containing tobacco. Any roll of tobacco

wrapped in any substance containing tobacco, which, of course,

if there appears some type of tobacco used according to

paragraph 4 [sic]. So the law says four -- five rules in the

law saying tobacco, tobacco, tobacco.

And now -- oh, okay. I have to push.

First, the cigarette, regular cigarette, is not the

product. As we all know, the product is the smoke. So the

tobacco has to go through pyrolysis and the -- smoke is what is

delivered. So, actually, cigarette is a smoke delivery system.

Cigarette smoke is, according to the pyrolysis, a very

complex, dynamic aerosol system of 5,000 or more components.

The cigarette smoke, this has a complex.

It's well documented that of these 5,000 components, there

are 60 very harmful and dangerous to health and either

carcinogen or co-carcinogen, et cetera. So the principle

"there is no safe cigarette" should prevail at least for the

time being. So the safe -- and I am talking as independent

consultant. I was in the industry in 1986. I have my own

international and local here, so that's my way of talking. I'm

not represent either way. No government, no e-cigarette, no

cigarette. It's my views based on my publication.

So there's no safe cigarette, and the best way to avoid

this health hazard is just simply not to smoke.

So let's go back to what we ascribe the cigarette to -- or

know now what is an e-cig? E-cigarette is a tube containing of

two parts. And I'm not going to go into the details because

you all know about that. One part is a liquid and the other

part is -- oh, that's it?

DR. DRESLER: Yes, sir.

DR. ABDALLAH: Okay, thank you. That's 3 minutes?

DR. DRESLER: Three minutes. It goes fast. I'm sorry.

DR. ABDALLAH: All right, thank you.

DR. DRESLER: I was thinking I was stricter yesterday last

session, and I should have announced that 3 minutes, when the

roller comes down, that's our 3 minutes. So we will stick

closely to that for our sessions.

Next, please.

MR. CONLEY: Good morning. My name is Gregory Conley, and

I am the President of the American Vaping Association, a

nonprofit organization that advocates for small and medium-size

businesses in the vapor product market.

My comments today revolve around a theme found in several

of yesterday's presentations that greatly concern me: the

failure to recognize that the toxicology of vapor must be

compared to cigarette smoke, not the use of no product at all.

With 99% of daily vapers being either smokers or ex-smokers, it

hardly makes sense to singularly focus on eliminating any

detectable levels of chemicals, especially when there is an

enormous risk that the regulation required to achieve such a

goal would also result in a net harm to public health.

Let's be clear. The greatest health benefit will come

from having products that smokers start using instead of

cigarettes, not from having over-regulated medicinalized

products that are safe but dull and unappealing.

So looking at the current market today, what are smokers

increasingly finding dull and unappealing, or at the very least

not satisfying enough to stick with long term? Closed-system

cigalikes. Several studies presented at SRNT last month add to

the growing body of evidence demonstrating that ex-smokers who

vape are far more likely to be using flavors in second- and

third-generation products, i.e., open tank systems and bottled

e-liquids, than they are cigalikes.

So why are so many activist researchers pushing for overly restrictive regulations that would squash premium vaporizers and e-liquid under the guise of ensuring e-cigarette products are safe? And why are so few people who call themselves public health advocates not expressing deep outrage and concern that the FDA's proposed deeming regulations would, by the FDA's own admission, wipe out 99% plus of nicotine-containing vapor products from the U.S. market?

Those who seek regulations that would eliminate or unduly restrict open vapor products should ask themselves why Reynolds American, the makers of Camel cigarettes, have similarly asked the FDA to ban all open system vaporizers, e-liquids, and most flavors. You're in bad company. The reason seems clear enough to myself and others. Removing the most effective products in helping smokers quit from the market will have the consequence of protecting the incumbent cigarette industry from competition from high-tech alternatives with superior characteristics.

Public health is about reducing disease and death, not eliminating all forms of risk from human life. Please do not forget this. Smokers and vapers, the true primary stakeholders in this debate, they're counting on you.

Thank you.

(Applause.)

DR. DRESLER: My next chair is empty. Is that you, sir?

(Off microphone comment.)

DR. DRESLER: Okay. Okay, so the next speaker, please --
yeah, step up. Sir?

MR. WEBBER: Is there a 6 or a 7?

DR. DRESLER: Yes, there is. Over there, but -- very
good.

MR. WEBBER: I had slides.

DR. DRESLER: Okay. And there, if you just push that
forward.

MR. WEBBER: All right.

Good morning. My name is Chris Webber. I'm here
representing Free to Vape, a national advocacy organization
representing tens of thousands of vapers coast to coast. I'd
like to begin by thanking the FDA for this opportunity and also
by asking everyone here to accept a simple fact. We're all
here today because we're united in our goal of ending tobacco-
related death and disease.

Free to Vape has submitted a total of 40,352 comments to
the FDA and 121,056 comments to Congress. The data is clear.

Users of vapor devices are overwhelmingly former smokers who use these products because they are concerned about the negative impact of tobacco use, and they use vapor products to decrease their tobacco consumption.

We are the individuals that proponents of strict vaping regulations are trying to protect. We are their statistics. Where they see numbers, we see friends. As these regulations primarily affect us, it is our fundamental right as American citizens to play the role in our own pursuit of health and happiness. Vapers are generally concerned that the FDA may base regulations on irrational fear instead of common sense. Proponents of strict vaping regulations often cite sensational studies claiming vapor devices may claim -- may contain dangerous chemicals such as formaldehyde. But as bona fide scientists, I hope everyone in this room can see these alarmist conclusions for what they are, driven by ideology and not by data.

Most recently, in an effort to further their personal crusade against anything that looks like smoke, many -- several researchers have moved beyond exaggerating data, and they've begun literally creating smoke where there is none. By misusing advanced vapor devices, some researchers have indeed

been successful in generating harmful emissions. However, we as vapers want you to know every single study demonstrating significant levels of VOCs in vapor share a fatal flaw: They ignore user input.

When a high voltage device is incorrectly paired with an entry level tank system, the wicking materials overheat to the point of combustion in what's known as a dry hit. A dry hit is accompanied by severely noxious taste and immediately results in discontinuation of use at that setting, something that even the most advanced smoking machine could never account for. Studies like these in no way prove that users, much less bystanders, are exposed to significant quantities of formaldehyde due to the vaporization of e-liquid. And regulated vapor devices, based on research like this, would be like regulating bread based on carcinogens known to be found in burnt toast. You don't eat burnt toast, and you don't vape a burnt wick.

We vapers know combustion equals cancer, and as a community, we're trying our hardest to avoid the inhalation of combustible materials at all costs. Our community is working hard every day to create the safest, most effective replacement for tobacco. And I'd like to call your attention to the screen

where you'll see one of the most recent advancements in personal vaporizing technology.

This is a temperature control device, designed specifically to avoid the noxious taste and the potentially negative health effects of dry hits. Under the current grandfather clause, however, this vastly superior device would be effectively banned and is a very real example -- the grandfather clause of the deeming regulations would directly and explicitly harm the public health, therefore must be either amended or stricken from the deeming regulations. Mr. Zeller has gone on record to state, and I quote, "If we could get all of those people who smoke to completely switch all of their cigarettes to non-combustible cigarettes, it would be good for the public health."

We're here to ask you that, or to tell you that, any regulations that stifle innovation of a variety of choice will harm the public health.

Thank you very much.

(Applause.)

DR. DRESLER: Sir? No, no. I'm sorry. You gave their -- thanks. Do you have slides?

MR. GODSHALL: No.

DR. DRESLER: Okay.

MR. GODSHALL: Good morning. I'm Bill Godshall, Founder and Executive Director of Smokefree Pennsylvania. Since 1990 we've campaigned to reduce cigarette smoking. In 2007 we convinced Senator Mike Enzi to amend the Tobacco Control Act to require -- put your warnings on all cigarette packs, something the FDA no longer deems or has never deemed important for public health because they've done nothing on it except when the proposed regulation was struck down for constitutional reasons.

In 2009 we urged FDA to keep e-cigarettes legal, and in 2010 we filed an amicus brief before the D.C. Court of Appeals in support of NJOY's litigation challenging FDA's ban, which was struck down as unlawful. Since 2011 we've opposed the FDA's proposed deeming regulation because it would create a huge black market by banning more than 99.9% of all vapor products currently on the market and because it would create an e-cigarette cartel controlled by big tobacco companies to market inferior cigalike products.

For disclosure, neither Smokefree Pennsylvania nor I have ever received any funding from any tobacco, drug, or vapor product company.

The scientific and empirical evidence consistently indicates that nicotine vapor products are 99% plus or minus 1% less hazardous than cigarettes and have never been found to be associated with any disease and pose no known risk to non-users. Nicotine vapor products have already replaced more than three billion packs of cigarettes, are nearly all consumed by smokers and ex-smokers who switched to vaping, and two new surveys found that three and four million U.S. smokers, respectively, are no longer regular smokers because of e-cigarettes, which are at least as effective for smoking cessation as FDA-approved NRT products, which have a 95% failure rate.

There's no evidence vapor products have ever created daily dependence in any nonsmoker, youth or adult, and there's no evidence vapor products have served as a gateway to cigarette smoking for any daily smoker anywhere in the world. Adult and teen surveys have consistently found that smokers were at least 20 times more likely than nonsmokers to report vaping, while adult and teen smoking rates have declined to record lows every year since vapor products began to skyrocket in 2008.

Public health benefits every time a smoker vapes instead of smoking a cigarette, and vapor products have similar risk-

benefit profiles as childhood vaccines, sewage treatment, and

condoms. But since 2009 the FDA has made many false and

misleading fear-mongering claims to confuse, scare, and lobby

to ban these lifesaving products under the deceitful guise of

protecting children and public health. Many FDA-funded funding

recipients also have made many false and misleading claims to

lobby for bans on vapor products and vaping.

Vapers and smokers have a human right to truthful

information about, and to legal and affordable access to, vapor

products. Consistently, the FDA has an ethical duty to

truthfully inform the public and to ensure that vapor products

remain legal and affordable. The deeming regulation is public

health malpractice of the worst kind because it protects

cigarettes and threatens the lives of millions of vapers and

smokers. The FDA should rescind its proposed deeming

regulation and begin telling Americans the truth about vapor

products.

Thank you.

(Applause.)

MS. KOVACEVIC: Distinguished audience, good morning. And

thank you for this opportunity. I am Patricia Kovacevic with

Lorillard Tobacco Company.

We are pleased to note that Lorillard's deeming rule comments proposing a series of workshops were aligned with FDA's thinking, resulting to date in two very informative workshops on the subject. Today I will share with you regulatory developments in Europe and brief considerations on the FDA proposed deeming rule.

In Europe, electronic cigarettes will be regulated consistent with the 2014 Tobacco Products Directive amendment, TPD. While concerns have been expressed regarding procedural and substantive issues surrounding the TPD adoption, it remains to date the most comprehensive legislative framework for e-cigarettes. Notably, TPD defines e-cigarettes as a new, non-tobacco category of products. A premarket notification must be submitted, although no approval is required. The proposed notification template adequately achieves public health goals by mandating full disclosure of product and ingredient information.

Furthermore, the European Committee for Standardization created an e-cigarette technical committee with the aim to develop European standards dealing with safety aspects of both e-cigarettes and e-liquid, as well as analytical methods, providing a basis for determination and quantification of all

chemical components stated in the requirements and related to the safety of those products. The British Standards Institute also opened for comment its electronic cigarette standard proposal.

Given the level of scrutiny of this industry, we and several other companies know our product well. Through its deeming rule, FDA must ensure that all products are held to the same standards of quality and ingredient disclosure. Registration, product listing, ingredient submission, and restrictions on youth access, among others, must be included in the first phase of the deeming rule and enforced.

However, due to limitations in the current state of science acknowledged by all here present, FDA should announce that it will exercise enforcement discretion over the requirement in Section 904 regarding HPHC reporting and the requirement in Section 910 for premarket review of electronic cigarettes.

FDA can and does exercise enforcement discretion as most recently it has done in the SE guidance published on March 5th. An enforcement discretion policy should continue while FDA, together with industry, academia, and the public health community, develops appropriate methodologies for evaluating

electronic cigarettes.

Thank you.

(Applause.)

DR. GOGOVA: Good morning. My name is Maria Gogova, and I'm Senior Principal Scientist at Altria Client Services. At Altria, I work on regulatory science issues on behalf of NuMark and Altria's other tobacco operating companies. NuMark markets e-vapor products in the U.S. under the brand name MarkTen. In 2014 NuMark acquired Green Smoke and its Green Smoke brand.

As with the first e-cigarette workshop in December, we believe that these meetings can facilitate the sharing of information between FDA, industry, and academic researchers on the important scientific issue related to e-vapor products. The e-vapor category is still new and evolving, but e-vapor products have shown promise as an alternative to combustible cigarettes.

The combination of innovative, potentially less harmful tobacco products and tobacco consumers' interest in them presents FDA with an unprecedented opportunity to reduce harm associated with tobacco use. As FDA considers the framework for regulating such products, the scientific evidence required should be flexible and consider all sources of available

evidence. FDA's existing draft guidance on PMTAs and MRTPs recommends that studies should be able to predict real-world outcomes.

We believe that a particular product or a product similar to the products already on the market, observations, and actual market conditions are likely to be more relevant than relying on estimates obtained from artificial experimental settings. For example, in-market studies may allow for the identification of most likely users of the product, transitions in product use behavior, and adverse events related to the use of the product. Further, FDA recommends studies to determine market appeal, attractiveness, abuse liability, and perception in order to assess the likely impact of a new tobacco product on initiation and cessation.

These measures, however, may not accurately reflect how individuals may use the product in the real world. There are many additional factors that influence the decision of a never user or a former user to experiment with the product or transition to regular use, making examination of these measures in nonmarket conditions extremely challenging.

The limitations of FDA's suggested approach can be offset by studying existing users of a product through the use of

validated survey instruments. These instruments could provide

FDA with a more accurate picture of how a tobacco product has

impacted the population as a whole. The use of multiple

sources of information when evaluating PMTs and MRTPs is

critical as it will allow FDA to better assess the risks and

benefits of tobacco product to both the individual users and

the population as a whole.

Thank you.

(Applause.)

MR. WOLFF: Hi. My name is Edward Wolff, and I'm

representing VIA, which is the Vaping Industry Alliance. And

because of the time constraints, I'm going to have to power

through these slides. Hopefully, there's some information here

that you'll be able to use. It gives a lot of information, and

once I get to the end, I would appreciate any contact.

The idea of VIA is to create a master product, and by

doing that, then multiple e-liquid vendors can meet the

regulatory guidance of the FDA. Now, there's a lot of

advantages to doing that because we all want the same thing.

We all want safe, legal, and adult products. Vapers want to

quit smoking; vapers have quit smoking. There's a lot of

people wondering if the scientific evidence suggests that

there's evidence of electronic cigarettes being -- showing that

they're -- allow people to quit.

Now, there's an overwhelming millions of people that show

you that, so if you have scientific data that is ignoring the

common sense, it doesn't make any sense. There's millions of

people that are vapers that have quit smoking and want others

to quit smoking. The FDA should maximize that and utilize that

because that is going to help with the mission of ending

cigarette tobacco.

A couple other things. The goal of the Act is to reduce

tobacco, and none of the NRTs have worked. I've tried them

all, and they're not effective. So, again, the FDA should be

looking at the nicotine delivery through electronic cigarettes.

One of the things that is not well understood is that the

deeming regulation says that all hardware without nicotine will

not be used in the deeming, it's outside of the deeming, and it

says it to the point where the FDA has not studied the cost of

that.

So there's a lot of hardware manufacturers that are not

here today because of the feedback that's been given out on the

deeming, so if there's any -- of the last conference, there's a

lot of people talking about batteries and safety and those type

of things. It's not in the deeming, and they say they haven't

studied that. If they are going to change that, there needs to

be a whole other process because those people are not here and

not representing themselves today.

On flavors, nobody likes tobacco, nobody. There's no

tobacco-flavored ice cream. All adolescents like the same

flavors as adults. So when all these arguments with flavors,

those arguments used to be against tiny cigars which the FDA

act allows. The FDA act does not allow for any flavors in

anything except cigarettes. They're trying to go after tiny

cigars. Flavors are used by adults and kids alike, but it's

not -- last thing, there's a lot of hijacked -- oh, sorry.

Advocacy by the chewing tobacco --

DR. MEINECKE: Good morning. My name is Gigi Meinecke,

and I'm a practicing dentist in Potomac, Maryland, and a member

of the Academy of General Dentistry.

The AGD has a long track record of supporting the role of

the oral health team in addressing the tobacco use of their

patients. Not only is tobacco use the leading preventable

cause of death and disease in the U.S., it also causes serious

oral health problems. A role of the dentist is to educate his

or her patients about prevention and treatment of tooth decay,

periodontal disease, tooth loss, and oral cancer. Since every

one of these oral health conditions can be linked to tobacco

use, we can be a strong message to our patients against using

tobacco products and offer guidance regarding smoking cessation

related resources, tips, and programs.

As dentists, we're especially concerned about the claims

that new tobacco products such as e-cigarettes are safe or can

reduce the risk of oral health problems and can help people to

quit smoking. The fact is, research to support such claims

hasn't been established. Further, early studies indicate that

e-cigarette use, especially among teenagers and young adults,

could actually lead to smoking regular cigarettes, a finding we

think is extremely troubling.

The lack of published literature makes it virtually

impossible to justify claims that these products are somehow

less harmful to the mouth than combustible tobacco products or

are without other adverse effects. The Family Smoking

Prevention and Tobacco Control Act gave the FDA unprecedented

authority to regulate tobacco products, including the latest

generation of products made or derived from tobacco and

intended for human consumption. The AGD urges FDA to use this

authority.

The AGD also wants to emphasize the critical need for research. Along with the ADA, the AGD strongly supports efforts to develop published research on the latest generation of tobacco products and the immediate and long-term effects of these products on oral health. To address this escalating public health issue, NIDCR is encouraging research on how the product components of e-cigarettes may harm oral tissues.

In FY 2016, the Institute will launch an initiative to encourage investigation of the biological impact of e-cigarettes on oral health, including the development of new tools and clinically relevant model systems to assess their effects on oral and periodontal tissues.

The rapidly increasing acceptability of e-cigarettes as safe products or as aids to tobacco cessation and their widespread use among smokers, nonsmokers, teenagers, and adolescents indicate a troubling trend that might pose a public health problem in the future. Without scientific consensus surrounding the effects of these products, it's impossible to generate evidence-based public health policies and regulations. Clearly, there's an urgent need to determine health impacts of e-cigarettes and other emerging tobacco products. With that said, we urge you to consult with the NIDCR as you assess the

impact of the latest generation of tobacco products on public health.

Thank you.

(Applause.)

DR. SUMNER: Hello. My name is Walton Sumner. I'm a family physician and health services researcher at Washington University in St. Louis. My colleagues and I have no conventional conflicts of interest.

In 2009 new vapers told us that they no longer needed nicotine first thing in the morning and they could work a shift, an entire shift, without it, if necessary. How could their answers to classic nicotine dependence questions change? Our research shows that nicotine forms nicotyrine when e-liquids are exposed to air and is aerosolized. Nicotyrine inhibits nicotine metabolism, potentially sustaining nicotine levels and explaining reported behavior changes; it might alter levels of cotinine as well. Most importantly, it might improve nicotine replacement products.

Let me explain how we arrived at our hypothesis. This is nicotine. Smoker serum nicotine levels make them unhappy, happy, sick, or dead. Smoking cigarettes causes spikes in serum nicotine. Most people clear rapidly because the liver

enzyme called CYP2A6 oxidizes circulating nicotine to cotinine and to 3-hydroxycotinine. CYP2A13 is a similar enzyme in airway epithelium that could oxidize nicotine before it reaches the bloodstream.

Nicotine is the only alkaloid in most new bottles of e-liquid. Partially used bottles also contain air; oxygen in the air changes nicotine to nicotyrine. The oxidation of nicotine to nicotyrine is slow but inexorable. Why does this matter? It matters because nicotyrine reversibly inhibits CYP2A13 in the airways and irreversibly inhibits CYP2A6 in the liver.

This leads us to our nicotyrine hypothesis. In smoking and perhaps some e-cigs, nicotine absorbed through airways could be oxidized to cotinine before entering the bloodstream, while nicotine absorbed through alveoli circulates into the liver, clears it to cotinine. The rapid cycle of relief and withdrawal reinforces smoking.

Cotinine levels conveniently correlate with smoking in serum nicotine levels. But clinically, first and second generation e-cig aerosols seem to deliver nicotine mostly to airways; when vaping e-liquids without nicotyrine, the vapor might absorb mostly cotinine. Serum nicotine levels remain low

and the vaper remains unhappy. In contrast, an aerosol with

nicotyrine inhibits both CYP2A enzymes. Nicotine absorbed

through airways escapes to the blood and is not cleared by the

liver. Slow nicotine clearance breaks the reinforcement cycle.

Cotinine levels are complicated but could be deceptively low.

Unfortunately, I do not have time to discuss supporting

evidence or testable predictions of the hypothesis, but here is

the most important implication. Combining nicotine analogs

with nicotine replacement products might work really well.

Imagine a lozenge that relieves nicotine craving for 4 to 6

hours. A handful could replace a pack of cigarettes. The

behavior changes that many exclusive vapers report may result

from CYP2A enzyme inhibition. I hope that we can learn from

e-cigs how to give everyone everywhere safe -- really, really

safe -- alternatives to smoking.

Thank you.

(Applause.)

MR. BALLIN: Good morning, everyone. My name is Scott

Ballin. I've been involved in tobacco control and public

policy issues weighted in and surrounding tobacco for about 40

years. And it's a pleasure to be here to talk a little bit

about e-cigarettes and how they fit into all the things that

are going on out there. As was noted in the announcement for

this workshop, the FDA feels it's important that gathering

information about the products, e-cigarettes, would assist the

Agency in carrying out its responsibilities under the law, so I

commend them for holding these three workshops on this issue

and encourage them to do more.

In the limited time that I have, I'm going to focus on the

broader cost-cutting issues that I think will assist the Center

and the various stakeholders in moving forward in what is a

dynamically and rapidly changing environment. Every year it

gets different, more complicated and complex.

First, I believe that Director Zeller is absolutely

correct in giving high priority to the establishing of a

workable and comprehensive tobacco and nicotine policy, and

which is based on the continuum of risk. While science is

going to be the driving force in setting new directions in

policy and regulations, we need to be careful in not becoming

so myopic that we lose sight of a more simple goal and

objective, and that is reducing disease and death caused from

tobacco use. So as the questions get asked and then answered,

let's make sure that the information we're getting is useful

for the development of policy recommendations.

Second, e-cigarettes and, in fact, all tobacco and nicotine products along the continuum of risk will need to have product standards set for them, and commonsense regulatory controls that reflect the risk of the product and that changing environment in which products are developed and then used. The combustible toxic cigarette should be the product by which all other products are measured and referenced. It will be contradictory to the objectives of the continuum of risk concept to set standards and regulations for products that are more stringent or less onerous than the deadly cigarette.

I've been working with the University of Virginia in trying to develop some commonsense approaches to getting people to engage in dialogue. I'd be happy to talk with people about those issues in addition to the science. It's looking at issues such as the definitions -- we have different types of definitions out there; how to develop a monetary and surveillance system; how to do more collective public and private partnerships in the area of research and many other areas.

So I'd like to talk with people about that approach because I think that dialogues like this in this room need to be done more at FDA and outside into the private sector.

Thank you very much.

(Applause.)

DR. THORNBURG: Good morning. I'm Jonathan Thornburg.
I'm Director of Exposure and Aerosol Technology at RTI
International, based in Research Triangle Park, North Carolina.
RTI is a not-for-profit research institute.

I'm here today to talk about some RTI internally funded
research on electronic cigarette emissions and user exposures.
And as part of this research, I want to declare I have no
conflicts.

The purpose of the research was to understand the
characteristics in gas emissions that are generated by
electronic cigarettes. So we understand the gas particle
partitioning within a user's respiratory tract. Our ultimate
goal is to use this data to understand what secondhand
exposures might be, because the only source of secondhand
emissions are the vapors that are produced or exhaled by the
users.

To do this work, we constructed a simulated lung in our
laboratory that mimics the physiological conditions within the
respiratory tract. We can control the temperature, humidity,
flow rate, flow velocities, and resonance time within our

system. We tested two different e-liquids: the Volcano tobacco

flavor and Volcano fruit punch using a second generation

cartomizer device developed by KangerTech.

Our results, preliminary results, are shown here, that

both the nicotine flavorings and artificial flavorings and the

preservatives are found in both the aerosol and the gas phase.

Our research did not focus on measuring any thermal oxidation

byproducts such as formaldehyde because others were doing that

research. However, we did try to assess the presence of

nonvolatiles like metals that might be produced by the heating

coil on our filter in our samples, but we did not find any of

those types of compounds.

This graph shows the size distribution of the tobacco

flavor aerosol generated by -- in our test system. The blue

line there is what you see in the normal room condition type of

conditions within our lung system. But when you put it in the

simulated lung temperature and humidity conditions, you can see

that you get the orange bar there, which shows that there is

some sort of active new nucleation of some micron particles due

to the presence of the humidity and the water vapor.

Again, just wanted to point out that the lack of particles

less than 100 nm shows that we were not producing any metal

nanoparticles in our system. We took this data to kind of

estimate what might be exhaled by a user, and we found that

more than 50% of exhaled -- more than 50% of the inhaled vapors

are exhaled by the user. And the chemical composition of these

vapors included both nicotine, the flavorings, and the

preservatives in the exact same ratios that were in the inhaled

fraction.

So I appreciate your time this morning, and I hope to be

talking more about secondhand exposures in the future.

Thank you.

(Applause.)

MS. SAVRANSKY: The American Council on Science and

Health, a public health education and consumer advocacy

nonprofit devoted to the promotion of sound science and public

health policy, urges FDA to promote the benefits of

e-cigarettes as a method of tobacco harm reduction in helping

smokers quit, and reconsider the deeming regulations. These

regulations would make e-cigarettes less accessible,

affordable, or attractive to adult consumers who choose

e-cigarettes as a safer alternative to smoking. Regulations

should be commensurate with health risk, and because

e-cigarettes are far less harmful than combustible tobacco

products, the regulation should take that into account.

Although we do agree that sensible e-cig regulatory measures are necessary, the requirement for manufacturers to obtain premarket approval of a new tobacco product application will limit the availability of e-cigarettes to those trying to quit. The FDA estimates that these applications will require thousands of man-hours of data collection and hundreds of thousands of dollars or more, a burden few e-cigarette companies will be able to bear.

Yet, the older, less reliable products entering the market before February 15th, 2007 will be grandfathered in under the Family Smoking Prevention and Tobacco Control Act. This applies to only about 1% of all e-cigarettes and vapor products. The only e-cigarette marketers with the wherewithal to comply with these onerous, needless deeming regulations would be big tobacco.

Our own research, published in a peer-reviewed academic journal, as well as many other studies and epidemiological data support the assertion that the methodologies comprising THR have the potential to reduce the tragic toll of cigarette smoking by supplying addicted smokers with a substance they crave, nicotine, at a much reduced cost in terms of adverse

health effects.

The currently approved cessation methods fail far too often, and the reduction in adult smoking rates is captured at 18%. We urge you to rely on the readily available scientific and empirical evidence, which is that e-cigarettes are far less hazardous than cigarettes. Regular use is confined exclusively to smokers and former smokers who quit by switching to e-cigs, and they have helped several million smokers quit or reduce cigarette consumption. And, most importantly, smokers smoke for the nicotine, but they die from the smoke.

Furthermore, studies have indicated that levels of the contaminants that e-cigarette users are exposed to are far below any levels that would pose a health risk, and exhaled vapor poses no risk to bystanders. The recently released federal survey Monitoring the Future found that youth smoking rates have continued -- or declined to historically low levels. Clearly, increased availability of e-cigs is not promoting an epidemic of smoking nor serving as a gateway. Making e-cigs inaccessible to desperate smokers by these needless measures will send smokers this message: Keep on smoking.

The likely outcomes is severe reduction in consumer choice, fewer quitting, and more preventable deaths. The WHO

predicts 1 billion prematurely dead from cigarettes this century if current trends continue. E-cigarettes present the best hope for averting this catastrophe.

Thank you.

(Applause.)

MS. SAVRANSKY: And I also have copies of publications that my organization has released.

DR. CHOI: Good morning. I'm here to talk about a vulnerable population: youth with asthma and their e-cigarette use. I want to acknowledge my collaborator, Dr. Bernat, at the University of Maryland College Park.

I'm here to present myself and standard disclaimer that doesn't represent the government. And if you have any questions about what I say, just call me or e-mail me; don't call my boss. I have no conflict of interest to report here.

So e-cigarette use has increased quite substantially among youth, particularly in the high school students, as so in here, in the graph, but little is known about e-cigarette use among kids with asthma. So this study is designed to answer this research question.

So data come from the Florida Youth Tobacco Survey. I would classify youth into whether they live in metro and non-

metro area with self-reported asthma status and also whether

they have an asthma attack in the past 12 months. We also

assess whether they have ever or currently use e-cigarettes --

I mean e-cigarette use in the past 30 days.

Now, here's the results: It's showing that -- shown in

two parts. The first part, looking at the metro youth. And as

you can see here, the figure shows that those who have been

diagnosed with asthma and report currently having asthma are

actually more likely than those who have never been diagnosed

with asthma to have ever used and also use e-cigarette in the

past 30 days. The situation is more prevalent in non-metro and

rural youth, as you can see in the bottom half of the graph.

The odds ratio of using, ever using e-cigarette or past 30-day

use of e-cigarette among youth with asthma living in a

non-metro area are much more likely than those who live in non-

metro area without asthma.

Then we explore the association between e-cigarette use

and susceptibility to cigarette smoking. Here the data shows

that among kids with asthma, those who have ever used

e-cigarette compared to those who have never used e-cigarette,

and those who use e-cigarette in the past 30 days compared to

those who did not use e-cigarette in the past 30 days are much

more likely to report a susceptibility to smoking. These are

nonsmoker, never try cigarettes, and have currently active

asthma.

Last, we look at the association between current use of

e-cigarette and reported having asthma attack in the past 12

months. The association here shows that those who reported

using e-cigarette in the past 30 days are much more likely than

those who did not use e-cigarette in the past 30 days to report

having asthma attack in the past 12 months. This is controlled

for demographics: their rural, urban, residential status; days

smoked in the past 30 days; and also exposure to secondhand

smoking.

So, in conclusion, we have found that e-cigarette use

among asthma is -- kids with asthma is much higher than kids

without asthma and associated with susceptibility to smoking.

And also it's associated with having asthma attack. We need

more research to understand why kids with asthma, a vulnerable

population, are more likely to use e-cigarette than kids

without asthma.

Thank you.

(Applause.)

DR. PHILLIPS: I'm Carl V. Phillips from the Consumer

Advocates for Smoke Free Alternatives Association, CASAA.

CASAA is an NGO dedicated to preserving consumer access to and

providing education about tobacco harm reduction, and is a

consumer membership organization with over 40,000 members.

Now, some of you might not be familiar with that word

"consumers." I don't think it came up yesterday.

Some common synonyms for it are "people" and also the

primary stakeholder in this process that you might never

realize it from this vantage. They are the ones who create the

demand that the secondary stakeholders, the industry that is

well represented in FDA proceedings, fulfill. They are the

ones whose preference to consume nicotine results in the

behaviors reported in the talks. They are the owners of the

lungs that were the subject of yesterday's scary bedtime story

about diacetyl.

You could have heard more about consumers and what they

have to offer this conversation. CASAA submitted five

applications to present at these two workshops, offered

presentations by leading experts on the topic who also happen

to represent consumers. All were rejected. Yesterday,

consumers of e-cigarettes were mostly represented as biological

nicotine processing systems and vaping machines. However,

those dehumanizing moments were actually a high point compared

to the frequent implicit reference to them as abusers.

When the preferences of consumers came up, it was

inevitably in the context of how they could be manipulated to

serve some ivory tower goal. For large portions of the

workshop and even more so for the first workshop in this

series, you might have thought we were talking about a

theoretical new product, not something that millions of people

are already using.

Indeed, the most striking feature of the first workshop is

that most of the supposed experts who were speaking could have

been replaced by a random pick from among CASAA's membership

and the quality of the information conveyed would have been

improved. This workshop was a big step up compared to that. I

think only three or four of the presentations could have been

improved by subbing in a random vaper.

Despite quite a few presentations here that were quite

positive about the products, I remain struck by the following

observation: We normally think of regulation as the government

taking action to protect consumers from the bad behavior of

companies, but in this arena we are disturbingly dependent on

companies to protect us from the government. We have to depend

on researchers from BAT, Lorillard, and others to protect us

from the propaganda coming from government agencies and

government-funded researchers. We depend on smaller innovators

to improve the products.

Listening to the presentations, you might think that

someone was proposing regulations that would improve the

quality of e-cigarettes and make them safer, but no such

regulation has ever been proposed. Instead, every proposed

e-cigarette regulation the world has seen is some form of

creeping prohibition that would hurt consumers rather than help

them.

(Applause.)

MR. ANTON: Good morning. My name is Mark Anton. I'm

President of What a Smoke, an electronic cigarette and vaping

company. During the past 50 years, the Surgeon General and CDC

have estimated 20 million Americans have died due to smoking.

We take seriously the complexities of how the FDA may combat

the issue of smoking-related deaths, but to categorize vaping

products as tobacco products is, at best, a public disserve.

The CDC says quitting smoking saves lives and improves health.

They say in doing so, one must resolve not to puff, not even

one. They also state that there is no safe cigarette,

electronic or otherwise.

We find this to be a direct contradiction of exactly the
tactile feel and sensation our customers seek out in their
desire to switch from tobacco leaf cigarettes, so how can the
FDA look at our products impartially? Since 2009 the FDA has
looked to ban, limit, and eradicate the use of e-cigarettes as
an unapproved medical device. And now to declare the desire to
regulate them under the Tobacco Control Act is curious, at
best.

The FDA, for years, has looked past the current available
scientific evidence and now seeks to apply their own science
with a severely skewed panel of scientists. One must ask, is
this in the public's best interest when current evidence found
e-cigarettes, a/k/a vapor products, are 99% less hazardous than
cigarettes, have never been known to cause any disease, are
virtually all consumed by smokers, have replaced more than 3
billion packs of cigarettes, have helped several million
smokers reduce or quit smoking, have never been found to create
nicotine dependence in any nonsmoker, emit trace levels of
nontoxic aerosol that poses no harm to non-users?

Youth and adult smoking rates and cigarette consumption
have declined every year since 2007 when vapor sales began.

Under the Drug and Cosmetic Act, the FDA is charged to promote

and encourage the development of innovative products and

treatments to achieve abstinence, reductions in consumption,

reductions in harm by providing open and working pathways for

products that come to market.

This obviously does not include e-cigarettes, for the

burden placed on tobacco products requires the following: For

the protection of the public health shall be determined with

respect to the risks and benefits to the population as a whole,

including users and non-users of tobacco product.

This is an ambiguous and extremely difficult standard to

reach, one that other nicotine-based products are not required

to achieve. If the FDA continues down this path, they are

destined to ban or hand over the industry to big tobacco

companies because they are the only organization that can

handle these standards.

Thank you.

(Applause.)

MS. HALLER-STEVENSON: Thank you. I am commenting on

behalf of the National Association of County and City Health

Officials, also called nay-cho, not na-cho. Thank you for

calling attention to these important issues that affect the

public's health.

NACCHO is the voice of over 2800 local health departments across the country. Local health departments are actually leading the way in establishing policies and procedures regarding electronic smoking devices in the absence of any on the national landscape in an effort to protect their own communities and create environments that are -- make it healthier -- make it easier for their people to be healthy. The most common approaches by local health departments have included creating a minimum age of sale for e-cigarettes and restricting the use of the devices in the same locations where smoking combustible cigarettes is already prohibited. NACCHO is eager to contribute to FDA's fact-finding effort on this issue and offers the following comment on today's topics:

There are currently no federal consumer protections in place to ensure that e-cigarettes are properly labeled and tested. One study of e-cigarette refill fluids found that more than half of the fluids tested deviated by more than 10% from the nicotine concentrations listed on the label. Because e-cigarettes are unregulated, there is a lack of credible information on the full range of chemicals being produced by the large number of different products on the market.

Warning labels have been an important source of information for tobacco users on other types of products, and as such, similar warning labels should be utilized for all electronic smoking devices regarding product contents and potential for harm. Use of electronic smoking devices by youth is dramatically increasing as well. From 2011 to 2012, use of e-cigarettes by middle and high school students doubled. One in three students surveyed reported that they perceived e-cigarettes as being less harmful than combustible cigarettes.

Because e-cigarette product packaging is not uniformly labeled and there is no federal law in place regarding age of sale, retailers are left to decide whether to restrict sales to minors. While companies may not encourage sales to minors and may even restrict that on certain packaging, on others it's not present and it really is left to the retailers to deal with that issue. Due to the potential risks for negative health effects and tobacco dependence, a national minimum age for sales should be established to limit e-cigarette access for youth.

With the fast increase in use of electronic smoking devices and limited regulation in place, NACCHO urges the development of consumer protections in the form of accurate

representation of product contents, health risk warnings, and

restrictions on minimum age for sale. Thank you for your

attention and for the opportunity to comment on this issue.

(Applause.)

MR. NITZKIN: Thank you for the opportunity to speak. I'm

Dr. Joel Nitzkin, a public health physician here on behalf of

the R Street Institute. The comments I offer here today are

entirely my own and do not necessarily reflect the policy

stance of R Street, the American Association of Public Health

Physicians, or any other organization with which I am or have

been associated. My purpose today is to urge FDA to consider

the potential benefits of e-cigarettes and to consider tobacco

cigarettes as the primary basis for comparison when dealing

with issues of toxicity and addictiveness.

The most recent CDC and other data, when taken in context

of all of the survey data together, demonstrate the potential

for e-cigarettes to be the ideal tobacco harm reduction

product. They satisfy large numbers of smokers without

increasing total use of nicotine by teens. The most recent CDC

data shows use of nicotine delivery products defined as use of

cigarettes and/or e-cigarettes by middle and high school

students declining from 2011 to 2013.

These and other data strongly suggest that e-cigarettes lead teens away from smoking with remarkably little recruitment of nonsmoking teens and remarkably little transition from e-cigarettes to tobacco cigarettes for teens or adults. These findings were reinforced by data presented at the recent SRNT conference.

The attitude of almost the entire public health community, including FDA, appears to be one of extreme distrust of what they refer to as the tobacco industry. This results in requirements for proof of safety and requirements relative to the impact on non-users so extreme that such proof is a near impossibility. Studies and survey data published to date are dismissed as insufficient for policy and regulation. I would like you to consider the possibility that this excessively negative attitude by FDA and others might reflect, at least in part, something other than zeal to protect the health of the public.

Decades ago, leaders of the tobacco control movement discovered that transforming tobacco control from a public health enterprise to a moral crusade against the evil tobacco companies resulted in substantially increased political and donor support and enhanced recruitment of energetic volunteers.

This, in turn, led to the goal of a tobacco-free society, a goal interpreted as ruling out any consideration of any non-pharmaceutical nicotine delivery product in any public health initiative.

My question to FDA is this: Does FDA share this commitment to a tobacco-free society, and if so, what does this imply for consideration of the potential benefits of e-cigarettes?

Thank you. I have a handout if anyone wishes additional information.

(Applause.)

DR. STOTESBURY: Okay. My name is Steve Stotesbury from Imperial Tobacco, and thank the FDA for this opportunity for comment.

Heated tobacco products have enjoyed a resurgence of interest in the last 18 months, and to some they offer, seem to offer, a similar potential as e-vapor products for risk reduction but with a greater potential consumer appeal. How should they be regulated and taxed relative to e-vapor products? In Europe, there's been a suggestion, for example, in certain countries, to tax heated tobacco as smokeless tobacco products. Is that the right approach?

Now, we've done some work to consider the potential impact of heated tobacco and e-vapor use on -- sorry, wrong slide. Imperial already has e-vapor products in its portfolio. We've begun a program of work to evaluate the potential of heated tobacco, and our early findings are instructive. Both e-vapor products and heated tobacco deliver in terms of reducing exposure to smoke constituents.

For the heated tobacco product, typical cigarette smoke constituents are still present, including combustion products such as benzopyrene and carbon monoxide, showing that some pyrolysis is occurring. For e-vapor products, on the other hand, it's a paradigm shift in the emissions profile. In terms of both the nature and level of aerosol constituents, e-vapor is clearly different from tobacco smoke. We've done some work to consider the potential impact of heated tobacco and e-vapor use on indoor air quality, and we reported these findings to SRNT last month.

Briefly, this figure shows mass spectrometric profiles of exhaled breath following a single inhalation event after product use, comparing conventional cigarette, iQOS, Puritane, and a nicotine inhalator. Heated tobacco gives rise to a profile comparable to that from cigarettes. However, the

exhalate following use of inhalable nicotine delivery devices is much less complex. This should have a positive implication for continued use of e-vapor products in indoor areas.

In summary, our data show that claims for heated tobacco need to be thoroughly evaluated. Heated tobacco does offer reduced exposure but does not eliminate exposure to tobacco smoke. And our findings demonstrate that e-vapor presents the best opportunity for harm reduction, and we do not see heated tobacco as a viable Plan B. It's vital, therefore, that regulation focuses on boosting consumer confidence whilst enabling further innovation within this sector. Thank you.

(Applause.)

DR. DRESLER: Okay, I believe that's all of the speakers that we have that were registered for the public session. Are there any that came in late with some -- we don't have?

Okay, if that's the case, then we're going to go ahead and move on to the next session before taking a break, so -- and we'll hope that the next speakers are there. I know that our next one is.

This session will be on the Health Effects in Users, and the first speaker, Dr. Brad Drummond, who is a pulmonologist at Johns Hopkins School of Medicine, will be speaking on the

Health Effects of E-Cigarettes: An Overview.

DR. DRUMMOND: Good morning. Thank you to the Center for Tobacco Products for giving me a chance to talk. I suppose I either have the easy or hard job today. I'm going to try to provide an overview of what's going to happen, or discussions that occur later this afternoon, regarding the health effects of e-cigarettes. And also, you know, sort of provide perhaps some context for where the discussions yesterday and today are going or have gone.

I have no financial disclosures related to the area of electronic cigarettes. These are my other disclosures.

And so the objectives today really are to, again, try to provide an overview of the discussion, just a framework, a 30,000 foot view, if you will, and I'm going to first talk a little bit about the health effects of nicotine and then review e-cigarette vapor, and then highlight some of the overviews and challenges of the data, specifically looking at illustrative examples from the lung function, cardiac toxicity, adverse effects, and then secondhand vapor.

Now, obviously this outline here represents really what's been discussed over the last -- yesterday, as well as will be discussed today, so my goal is not to provide a summary of the

evidence but rather to provide -- pull out some examples from the literature and then provide how these examples may discuss -- or may frame the discussions that we're having today.

So it's important, I believe, as we talk about, in the context of electronic cigarettes or electronic nicotine delivery systems, that we don't forget about the fact that there's the nicotine component. There's been a substantial amount of discussion regarding the potential harms or lack of harms regarding the e-cigarette vapor, but I think first off we have to frame the context about nicotine, and obviously there was discussion yesterday about nicotine pharmacokinetics with electronic cigarettes.

But, you know, nicotine, again, as we all know, is an addictive alkaloid. As far as the harms of nicotine regardless of the delivery system, there are well-documented studies of the transient increase in both heart rate and blood pressure, the coronary and uterine vasoconstriction, and this may reduce coronary blood flow. And also it could potentially impact the risk of low birth weight children. There are data that suggest that nicotine, on its own, can alter thrombosis risk and also impact fetal and potentially adolescent brain development.

So in the context of when we think about the harms of

electronic cigarettes to the user, we also have to think about

the harms of nicotine. And this discussion gets complicated

because, as we've heard yesterday and as we've heard in the

prior workshop and as we'll hear later today likely, that the

nicotine delivery within the electronic nicotine delivery

systems is heterogeneous. And so when we think about, from a

scientific standpoint, assessing the harms of electronic

cigarettes, we add a whole other layer of challenge as we talk

about assessing the harms of nicotine in this user and then

also assessing the heterogeneous nicotine delivery.

Several mini-studies too numerous to cite here -- again,

this is purely for illustrative example -- have demonstrated

that the levels of nicotine and a certain number of puffs can

range widely. The serum nicotine levels are not only impacted

by the device itself, but also by the inhalation topography of

the user, as we heard yesterday.

So this is a tremendous challenge when we try to study

these devices scientifically to understand these harms because

of the heterogeneous nicotine delivery. And so I think that as

we frame the context of these discussions about how we inform

harms, we have to think about how this nicotine delivery may

make that a more complex endeavor.

At least one slide about acute nicotine poisoning, which is not perhaps relevant to the nicotine user but may be relevant to some of the other FDA mandates. Certainly, there's a risk for poisoning from the electronic cigarette, as we know that the nicotine from e-cigarettes can be absorbed by both ingestion, inhalation, or dermal absorption. And depending upon the data that you study, you'll read anywhere from 0.5 to 1 mg/kg of body weight can be lethal to an individual. And, typically, some of the replacement cartridges -- although again, there's tremendous heterogeneity in this, so this is a blanket statement -- they contain somewhere between 6 to 24 mg of nicotine, and potentially, as a hypothetical, a 30 kg child who swallows the contents of a 24 mg cartridge are at high risk for at least acute and lethal poisonings. And so I think that it's important to consider the role of nicotine in this context as well.

So what about the toxicology of electronic cigarette vapor? Again, this is a topic on its own, which has been dedicated -- several discussions previously. This is just a representative example of the fact that electronic cigarettes do -- vapor does contain toxic compounds. These are the similar compounds which are those that are absorbed in

combustible cigarettes, such as the carbonyls: formaldehyde,

acetaldehyde; the volatile organics such as toluene, propylene

glycol, and glycerin. There are tobacco-specific nitrosamines

which are detectable, as well as some heavy metals, and

obviously nicotine in the fine, in ultra-fine particles. As

many of the speakers in this morning's session have already

discussed, it's important to think about these toxic compounds.

Was our -- is our referent room air, or is our referent to the

combustible cigarette?

So this publication actually looked at how do these toxic

compounds compare to those seen in combustible cigarettes. And

you can see from these data that the levels of toxic compounds

seen in e-cigarettes were significantly lower than those

observed in combustible cigarettes on the order of 9 to 450-

fold lower. The authors -- this is just a quotation from their

publication -- state that "The vapor generated from electronic

cigarettes contains potentially toxic compounds," but "9 to

450-fold lower than those seen in smoke from conventional

cigarettes." So these data, my interpretation of these data is

that they do suggest that electronic cigarettes do contain

toxic compounds, they do seem to be at levels that are lower

than combustibles, and this would suggest that potentially that

electronic cigarette vapor may be less harmful than combustible

cigarettes. The caveat to that, however, is to recognize that

there are no established clear levels of safety for these toxic

compounds, so how much is enough or how much is safe remains

unclear. So I think that this is a good example of a

publication that does ascribe both value to those individuals

who view that electronic cigarette vapor is harmful and those

who ascribe to the perspective that the data is inconclusive.

It's also important, as we heard yesterday and in the

prior workshop, that all e-cigarettes are not created equal,

that there's the modifications in the voltage system, the tank

systems which contains variable voltage batteries. There are

recent publications, again although this data is not, I think,

established firmly, that higher voltage may increase

formaldehyde, acetaldehyde, and acetone levels; and how these

translate to harms to the individual user remains unclear. I

don't think that that data has been conclusively shown. We've

also had discussions about the role of flavorings, so cinnamon-

flavored refills, just as an example of the publication, remain

cytotoxic to embryonic and adult cells. Again, how this

translates to the user still remains clear [sic], but as we

assess the individual -- or the potential for harm to an

individual, as we'll hear about from these other discussions,

we have to recognize that in addition to the heterogeneity of

the nicotine delivery, in addition to the implications of our

perspective of the toxicology, also the fact that the data

that's published may represent data that doesn't reflect what

users are actually using at this point. So, again,

unfortunately, the message I'm painting is one of uncertainty

in the current data that's available.

So I'm going to sort of walk through some of the different

organ systems, and each one of these will be discussed in more

detail by the following speakers. But, again, just to

highlight a representative example of the data, so what about

e-cigarettes and lung function? I'm a pulmonologist, this is

what I care about, but I'll try to be unbiased. So

e-cigarettes and lung function. Again, most of the studies

have focused on the acute impact of e-cigarettes on active and

passive -- or excuse me, active and passive e-cigarette use on

lung function. There are very few effects, I would say almost

none, although we'll hear more data about this, about the long-

term effects on lung function of e-cigarette users. So as an

example, again, just a representative publication, this

publication looked at 15 smokers, combustible smokers, and 15

never smokers, and they exposed them to either combustible

cigarette exposure -- all directly for the smokers or

indirectly for the nonsmoker -- and then also e-cigarette

exposure. And they did, if you are an active user, 30 minutes

or 1 hour for passive exposure, 7 day washout, and then they

did spirometry testing, which is a measure of lung function

both before, immediately after, and 1 hour after the testing.

Excuse me, after the exposure.

And these are the data that they showed. And so the three

bars here, the control group, the tobacco exposure, and then

the e-cigarette exposure for those who are directly using them

or those who are exposed to secondhand exposure. The white

bars represent their FEV_1, which is a measure of lung function,

the forced expiratory volume in 1 second. The white bars were

the pre-exposure, the black bar was immediately after, and then

the gray bar was 1 hour after.

Now, I can tell you that as somebody who is an

epidemiologist, the first thing I notice is the wide standard

error bars in this graph, and I chose this example to highlight

this. One of the challenges of interpreting this literature is

that there's just under-sampling and under-powering of these

studies. So, for instance, in the study you can see -- and I

believe that the conclusions, which are correct from these data, suggest that e-cigarette use does not have a substantial change in either active or passive -- or excuse me, active or passive exposure to e-cigarette use does not have a substantial change in acute lung function. Now, that's hard to derive that that's a conclusive scientific truth from these data, but these are the types of data that we're asked to interpret as scientists.

So what about for other passive -- active and passive exposures? Again, studies have looked at the peak expiratory flow, other measures of lung function like forced expiratory flow at 25 to 75% of a range, the fraction of exhaled nitro oxide with tobacco and e-cigarettes, and it appears that there's no difference in active or passive exposures with e-cigarettes. So most of the data concludes that e-cigarettes may generate smaller acute effects on lung function than conventional cigarettes, but again, the data are limited by small sample size and also the type of device study. And I think we'll hear more about this from Dr. Bailey.

What about cardiac measures? Similar story. Nearly all data are acute studies, and a lot of the concerns that health advocates have are long-term outcomes. E-cigarettes are

associated with increased diastolic blood pressure, variable

effects of heart rate, decreased left ventricular function;

again, mostly small studies, mostly acute. And one of the

challenges in these studies is how do we disentangle the

effects of the e-cigarette vapor from that of the actual

effects of the nicotine? And we'll hear more discussions about

the cardiovascular effects of electronic cigarettes forthcoming

this afternoon. So just to sort of frame this discussion.

Secondhand vapor exposure, also something of interest.

There are studies that have demonstrated, cited here, that

demonstrate that the exhaled vapor does have detectable

nicotine concentrations and detectable $PM_{2.5}$, which is small

particular matter. There's also increased particulate number

in concentration. And it's unclear how these translate to the

secondhand exposure -- exposee, if you will. But there are

data that these chemicals are detectable in the vapor. It's

also, as recent publications have shown, that potentially the

aerosol from tank devices do include formaldehyde and

acetaldehyde, although clearly these levels are lower than

those emitted from sidestream combustible smoke.

So what's known about adverse effects of e-cigarettes?

There have been two recent publications late in 2014 that have

tried to perform meta-analyses of the adverse effects in the

published literature, and that's, I think, the most appropriate

thing to do given that most of these studies are small studies.

And there were no serious adverse effects in controlled

prospective reports. The most common effects were mouth and

throat irritation somewhere in the order of 17 to 32%, cough,

nausea, and most of these effects were short term.

Importantly, as discussed previously, it's unclear -- the data

is limited by the lack of a clear comparator group or a uniform

comparator group. Are we looking at these adverse effects

compared to smokers, or are we looking at these adverse effects

compared to never smokers, which I think is an important

contextual discussion to have. Also, there's concern for

possible selection bias from cohort studies. So are these

individuals who are reporting use because they are pro

e-cigarette, or are they individuals who have somewhat of an

equipoise about the self-reporting of their e-cigarette adverse

effects? Again, one of the challenges of interpreting these

data.

What about cessation? We're going to hear later on this

afternoon about e-cigarettes and cessation, so this will not be

a comprehensive review. But there have been studies of both

individuals who I call the unmotivated quitter, meaning
somebody who is unable or unwilling to quit smoking combustible
cigarettes, and then there are those who are trying to use them
as a cessation tool. And there are several studies that have
demonstrated there's favorable modification in smoking habits
and trends in cessation rates among e-cigarette users who are
not interested in quitting combustible cigarettes. It's
unclear, the long-term implications. The longest study I've
seen is 24 months.

Clearly, we want to know what's going to happen to these
individuals long term, so I think that data is also
inconclusive. And then as far as e-cigarettes as a primary
cessation tool, to my knowledge -- well, there's been limited
studies comparing e-cigarettes to FDA-approved cessation
therapies, and to my knowledge, I haven't seen any data that
shows that e-cigarettes are superior to FDA-approved therapies.
Again, we can also ask ourselves what is the appropriate
comparator group for that benchmark.

So this is what I think the real challenge is. This is a
recent meta-analysis that was looking at some of the outcomes
related to electronic cigarettes. It's purposely small; you
don't need to be able to read it. But these are the types of

studies we're trying to derive data from: 32 smokers,

30 smokers, 15 smokers, really small studies to try to

understand long-term health effects from heterogeneous exposure

in a heterogeneous population with heterogeneous use patterns.

And so this is one of the challenges, I think, when we think

about how do we assess the harms of electronic cigarettes in

the individual user.

So where is our current state of knowledge? Well, I think

that the data for organ-specific effects are lacking, not for

lack of trying. There were limited data with lung function

decline, long-term cardiac toxicity. Malignancy risk has

virtually been unexplored at this point, and we're going to

hear later about biomarkers for use and disease associated with

electronic cigarettes. I also think that we need to focus

somewhat on certain adverse groups. We've heard briefly this

morning and we'll hear later about the harms associated with

electronic cigarettes and asthmatics. We'll also hear about

pregnancy and then potentially also about dual use from

combustible and e-cigarettes.

So I think with that, I'll stop, and we'll move on to the

next speaker. Thank you.

(Applause.)

DR. DRESLER: Thank you.

We're going to have a little bit switch-around in the
order, and so our next speaker is going to be Dr. Bhatnagar
from the University of Louisville, and he will be speaking
about Cardiovascular Effects and Potential Cardiovascular
Disease Risk Associated with Electronic Cigarette Use.

DR. BHATNAGAR: Well, good morning, and I want to thank
the organizers for giving me the opportunity to come and
present the work. I have no disclosures except that our
tobacco center is being funded by the FDA.

What I wanted to do this morning was to talk to you about
the cardiovascular effects of e-cigarettes. I'm sure you heard
a lot about what these things are, what they contain, and a
detailed discussion of what the relative toxicity would be. So
what I wanted to do was to frame the discussion in terms of the
cardiovascular effects and what it means from a cardiovascular
perspective.

I'm sure you've seen this slide many times, but I just
wanted to put it there to maybe make the point that all the
toxicity and the health effects are dependent upon the device
and the nature of the device, and there are many types of
devices; this is one of them. But there are many types, and

they are used in different ways and contain different

ingredients, and as a result, their effects are likely to be

different. And as was pointed out just before this talk, this

is a heterogeneous sort of type of exposure, and we are trying

to understand what this heterogeneity means and is it -- how

important this heterogeneity is, or are there some underlying

set of common principles, some commonality in which there is

sort of a similar exposure from which we can deduce some of the

important effects, particularly in terms of the long-term

effects and in terms of the physiological effects on the

cardiovascular system.

So the e-cigarettes don't contain a whole lot of things,

but they do contain several important things, and I wanted to

sort of go through each one of them and sort of evaluate their

cardiovascular risk and impact. They contain nicotine and, of

course, they contain propylene glycol, and some of them may

contain variable levels of glycerol. And nicotine is heated

and vaporized but in most cases not burned, but although there

is some -- may be some pyrolysis. There are levels of most of

the chemicals that have -- or even cancer effects on low. And

there is this lively debate how about low it is and what is the

level of harm reduction that's actually possible with the

reduction of different types of constituents.

And, to date, we have lots of literature showing that there is lower levels of XYZ chemicals but very little understanding of what actually these decreases mean and what their health impacts might be. And to make matters worse, these things vary with the duration and use and the type of use the devices are put to, and so therefore, these things can change depending upon the use pattern. They do contain levels of aldehydes and particulate matter, or PM, and these are some of the things that are of chief concern, particularly given the vast amount of literature that has accumulated upon, relating to the effects of PM and aldehydes on cardiovascular tissues.

So, of course, you heard that nicotine is the primary constituent, and of course, that's the reason that these products are being used. They contain low levels of -- the e-cigarettes contain low levels of carcinogens. They have trace levels of different nicotine sort of co-contaminants or nicotine-related compounds. And they contain variable doses of nicotine that are variable.

As you've heard before, I'm sure many times, is that nicotine is not an innocuous drug, and particularly in terms of cardiovascular effects, it has sort of significant effects on

blood pressure, on heart rate, and in cardio function. It also could affect cognition and appetite, and it can affect release in metabolism neurotransmitters such as dopamine, norepinephrine, and epinephrine in terms of cardiovascular effects.

It is particularly significant to point out that nicotine could have a pro-angiogenic effect, and what that means is that it can promote the growth of blood vessels, and so that could increase atherosclerotic lesion formation, for instance, or would be able to cause an increase in cancer development because endogenesis is required for tumor genesis. But given what else is contained in actual tobacco products, nicotine is relatively less toxic, but the long-term effects remain unknown. And there has been this debate that there are approved nicotine replacement therapies and have been better tolerated for use of many people for long periods of time, but it's not clear whether the mode of delivery is similar with the NRTs as it is with e-cigarettes and whether the pharmacokinetics of nicotine matters, and whether there is a spike in the levels of nicotine that could be achieved especially with the newer generation e-cigarettes would be similar or different from the effects of other NRTs.

Of course, to carry the nicotine, the e-cigarettes contain propylene glycol and is generally considered nontoxic. There are some studies dating back from the '50s and '60s, exposed rats for over a year, found relative low toxicity, and it's been approved by the FDA as a solubilizing agent for different types of medication. And so the general idea is that there is -- this is not a very toxic compound, but the old toxicological studies are very superficial, looking at some cancer development and so on, and certainly no cardiovascular effects were evaluated. So we do not have really good animal data showing what the effects of propylene glycol might be and how it might affect cardiovascular function not only at baseline but also during disease development, so that's sort of some area of future investigation. It's used generally in theater fog and in the aviation industry, and there's been some mild effects such as eye and respiratory sort of irritation have been noted.

And it could be of concern in a susceptible population, particularly people who have asthma, particularly also maybe people who have unstable plaques because people with unstable plaques have -- are very prone to stresses and to levels, some levels of irritation. And so susceptible populations may have

higher sensitivity due to propylene glycol. And,

unfortunately, in some studies, there have been some ethylene

glycol, which is in antifreeze, has also been detected, at

least in the first generation products but not so much in the

newer generation products. They do contain a level of

different types of aldehydes and other volatile organic

compounds, as well as very, very low levels of trace metals

which are in some studies similar to background levels, and so

it depends upon the product and how it's been used. There have

been some sort of trace contaminants that have been noted.

A primary concern has been, in the literature, the

aldehydes and formaldehyde, acetaldehyde, and acrolein. And in

some cases they could be sort of very, very similar to -- the

levels would be similar to those present in conventional

tobacco and so particularly in conditions where there is a high

pyrolysis, high levels of heating, and so there is degradation

of propylene glycol and glycerol. And this generates -- these

compounds, which are of primary interest, at least in terms of

cardiovascular toxicity, glycerol, for instance, generates

acrolein, and propylene glycol can generate metal glass and

formaldehyde and acetaldehyde.

From our point of view, the development or the generation

of acrolein is particularly significant because acrolein is at least an order of magnitude much more toxic or much more reactive than formaldehyde and acetaldehyde, and though there is much research or much debate and work, sort of debate focused on formaldehyde and acetaldehyde, I think the -- even low levels of acrolein could be particularly toxic. And since acrolein may be primarily derived from glycerol, maybe one way of preventing the formation of acrolein is to sort of minimize the use of glycerol in e-cigarette liquids.

The aldehydes have been measured not only during heating, but also in the e-cigarette juice or the liquid itself, even before it's been used, and the levels of different aldehydes, particularly acetaldehyde, crotonaldehyde, and formaldehyde are present in significant levels in these e-cigarette liquids. Crotonaldehyde -- so acrolein is a three-carbon aldehyde, and so we call it an unsaturated aldehyde, makes it very reactive. It reacts with duratyone (ph.) and amines and a variety of different nucleophilic compounds in the body. And crotonaldehyde is just a 4-carbon -- it's a 3-carbon, but it's also an unsaturated aldehyde, so again it's an order of magnitude much more reactive than formaldehyde and acetaldehyde.

So given that all these aldehydes are present, it may be -- so we try to figure out whether or not some of them will be more toxic than others and what is the level of risk that they might impart. And this could sort of vary depending upon the type of cigarette that's been used. And here is a list of some different e-cigarettes that was in the study from Japan showing that there are different levels of acrolein from that range from being sort of undetectable to almost to the level similar or at least in the same range as in conventional cigarettes, and this depends not only on the type of serums, also its use. And so the amount of these aldehydes that are generated may depend upon the amount of air that's actually delivered into the device and so initially -- and some of the studies have done that, is initially they would measure e-cigarettes and say well, there are no aldehydes because if you started with a new, fresh cigarette, then -- or a fresh e-cigarette, then you get low levels of aldehydes, but as you actually -- after repeated use, and these are showing the different puffs, that you see that the levels off of the aldehydes increase. And after some levels, the levels of formaldehyde could be comparable or higher than conventional cigarettes, and the same goes for acrolein.

And this is -- I'm sure many people have seen this study which created a lot of ripple in the media, which was that there are high levels of formaldehyde that are generated in e-cigarettes, but the caveat was that this was at a very high voltage, and then most people would not actually use this voltage, and so therefore, this may not be a valid statement saying they regenerate mega levels of formaldehyde. And even so, formaldehyde is -- although it's a potential carcinogen, it's not something that causes lung cancer, and it causes, in very high doses, nasopharyngeal cancer, and so we're not sure whether the risk that is -- because formaldehyde is attributable to the risk of smoking. In other words, that -- or the risk of smoking cannot all be attributed to formaldehyde. And so maybe there are other reasons why tobacco smoke is so bad and formaldehyde may not be the main culprit. So then what is the main culprit?

So this is an example of the type of risk assessments that people do, and this risk assessment is based upon the relative toxicity of a compound and its effects and its concentration. So what makes a poison is the dose, so if something is very, very reactive, it could be very toxic in low doses, and some things that are less reactive may not be very toxic even at

high doses. So if you do a relative risk assessment, this is

from conventional cigarettes, then we find that more than --

about 88% of the risk could be just attributed to acrolein

alone. And so even though conventional tobacco cigarettes

contain, you know, 7,000 different chemicals, not all of them

might be equally of equal import, at least in terms of their

toxicity. So if acrolein is the main sort of constituent that

may be responsible for harm, then maybe regulating the levels

of how much acrolein is generated may be one way of approaching

the sort of harm reduction category. And the reason we're

interested in acrolein is because studies have shown that mice,

when they're exposed to acrolein -- and this is about the level

similar to present in regular cigarettes -- that there could be

an increase in their atherosclerotic lesions, and you can see

that here.

This is just the lesion area, this is the aortic valve in

the heart, and we're showing that there's a development of

lesions here and that you could see much greater plaque

accumulation in mice that were exposed to acrolein, so again

suggesting that acrolein could indeed be toxic and have

cardiovascular effects. In addition, it is -- if you have sort

of a developed or advanced plaque and then you expose that

plaque to acrolein, you can see that becomes unstable. There

are some things called the MMPs, the metalloproteinases, that

cause the degradation of the plaque. And there is this idea

that, at least in the cardiovascular literature, most of the

effects of smoking are proximal, that exposure to smoke just

prior to a plaque-rupturing event is much more significant than

prolonged exposure, so the acute events are triggered sort of

acutely by exposure to tobacco smoke. And so if there are low

levels of acrolein and other constituents and aldehydes that

are present in tobacco smoke, as well as in e-cigarettes, then

that might trigger the destruction of plaque. There could also

be a genomic component of that because if there is some

irritant receptors that are activated, that could lead to

plaque rupture or even to sudden cardiac death.

The other constituent that is of high interest is PM, and

as you've seen in other presentations, that e-cigarettes

contain particulate matter, and the size and distribution is

similar to that present in cigarettes. Now, most cigarettes

have actually perfected a range of $PM_{2.5}$ to the level that it's

easily inhaled and goes to the lung so it doesn't cause

coughing or irritation, and so that carries nicotine into deep

lung. But those particles are combustion particles, and they

contain carbon, they contain levels of metals and so on,

whereas the particles that are present in e-cigarettes are just

supersaturated with steam or with propylene glycol or vapor.

Now, the debate is that whether the particles that are

generated contain only sort of propylene glycol, which is less

than aerosol, or is it as toxic as a particle that contains

sort of carbon-based particles present in the ambient air or

present in tobacco smoke. The answer is not clear, but it's

been suggested that maybe the constituent of the particle may

not be that important as just the particle size itself, and

that there may be some autonomic receptors that are triggered

because of these particles and that they would be then leading

to adverse cardiovascular events.

So direct effects of e-cigarettes have been documented in

several studies, you heard some of the examples before, and

there are very, very minimal changes. But these are early

studies done in very small groups of people, and there is some

indication that it may lead to sort of pulmonary inflammation,

but that also is not very clear. But they have this variety of

constituents, and the challenge is then to understand what

effects may be long term and what effects may be in susceptible

individuals. And certainly no long-term studies are currently

available. But one of the issues that arises -- and we've

heard this today this morning, and we heard it repeatedly

yesterday and in the first workshop -- is that there are levels

of different toxicants are much lower in e-cigarettes than in

conventional cigarettes. And so people come to the conclusion

that e-cigarettes would be less toxic than normal cigarettes

because if you were -- and most simplistically think of this as

a linear dose-response relationship, so the less the

constituent, the less the toxicity.

But extensive work both from tobacco exposure as well as

from exposure to ambient particulate matter has shown that the

dose-response curve may be nonlinear and that you -- at very,

very low levels of exposure, you accrue a significant level of

harm. So, in this example, it shows that at least 80% of the

harm of smoking, say 20 cigarettes a day, is accrued by smoking

less than 3 cigarettes a day. So if we quantitatively look at

the problem and try to understand that in e-cigarettes we have

20% of the toxicity and this 20% of the toxicity is accounting

-- it should be much less, or 20% less people, 80% less people

should die may not be true for two reasons: first, because of

this nonlinearity of the dose-response curve and the usage. So

if you're using the same thing twice as much and it's half as

toxic, you come to the same place. So it is not very obvious

that reduction of X amount or some percent actually translate

into reduction of that level of harm.

So, in sort of conclusion, we need to worry about what

e-cigarettes would mean in terms of cardiovascular health, and

sort of the idea is that maybe they would sort of reverse the

social norm and at least have the potential to reverse the

social norm and sort of erode all the gains that have been made

in containing sort of tobacco exposure and in deducing the

death and disease, particularly cardiovascular death and

disease, associated with increased tobacco use. We do not know

how much it's been used. There's some indication that most

people who are using it are already smokers and they sort of

are -- they're the dual users, may be prevalent or at

moderate/high levels or may be not as prevalent, so I think

there are still studies that are necessary to understand and to

figure that out.

Some surveys have shown -- and I think you will hear this

from Chris later on, is that they could be effective devices

for sort of cessation. And certainly, in the time that we do

not know how effective they are, we cannot carte blanche assume

that they are bad and then be totally intolerant to it, but

looking at this dispassionately in a disinterested manner, that it would be that we need to evaluate and have sufficient evidence that they are indeed reducing the amount of harm, particularly both in terms of cardiovascular effects and in terms of cancer effects. And particularly concerned about cardiovascular effects because they appear at much, much lower dose than the cancer effects, and so therefore, if there is sufficient harm reduction, the claim to harm reduction, then we would like to see rigorous and robust cardiovascular data.

But we have still much more to learn, and particularly, we need to understand what are the acute effects much more clearly. We need to understand what the long-term effects may be even though the devices are changing, even though the user use patterns are changing. We cannot, you know, throw up our hands up in the air and say this is sort of an impossible-to-study problem. We have to figure out ways in which we can sort of account for the heterogeneity changes and pattern of use, changes in device manufacture and so on, and how that might contribute. We need both long-term animal studies and long-term human studies. We need to understand what is the addictive potential of these devices and how they are being marketed and how things have been communicated, and whether

they've been used to deliver things that are not intended to be
delivered by these devices.

Thank you.

(Applause.)

DR. DRESLER: Thank you.

Okay, we'll go to our next speaker, and the next speaker
is Dr. Kumar from Ohio State University, ENDS and the Oral
Microbiome.

DR. KUMAR: So I'm sure most of you are wondering, you
know, bacteria and e-cigarettes, really, will people study
anything? So I'm going to start by trying to see if I cannot
convince you that the oral microbiome is really important.
Bacteria keep you healthy. And that evidence comes not just
from the oral cavity, but a lot of the gut microbiome work is
moving us in that direction, so bacteria have made the cover of
29 of our very popular magazines from the *Wall Street Journal*
to *Science* to everybody. Most of our presidents don't have
that honor, so bacteria are clearly important to us. Bacteria
does some very important things to us. One of them is that
they keep us healthy. So they do what's called -- they prevent
pathogens from colonizing.

There we go. Now that I know how to play with this -- or

not. Well, what did I do? There. This is --

DR. DRESLER: Don't use that one, just use that one.

DR. KUMAR: Okay. But this isn't moving.

DR. DRESLER: Yeah, you get -- and it's like always when you come up on a podium, you know how it messes up, so --

DR. KUMAR: That's all right, that's all right. We don't need it, we don't need it.

So commensal bacteria keep you healthy. The first thing they do is they prevent your pathogens from colonizing, so if you can think of your bacteria as your lawn in your home, your lawns are made up of one species of grass. That keeps your lawn healthy, it keeps, you know, the weeds and the African violets from colonizing, and that's what your bacteria is, it is your own lawn inside your body. And bacteria come into your body long before your immune system kicks in, so basically these bacteria train your immune system to recognize who is a friend, who to keep, and who is a foe or who is a pathogen. Commensal depletion has been associated with several, several diseases. Evidence is emerging about, you know, the associations between obesity and commensal depletion, neurological deficits, and metabolic deficits. We just published a paper, it's called "Mouth Guards," it's just a play

on the word "mouth guard" because, you know, we are talking

about the role of the indigenous microbiota in maintaining oral

health.

Our interest in bacteria were piqued when we did the

study. We were looking at when these bacteria are acquired.

So basically we looked at four groups of people: babies without

teeth, 1, 2 -- you know, between -- under 6 months of age;

babies with milk teeth; kids who are transitioning from milk

teeth to permanent teeth; and then adults with permanent teeth.

And then we collected samples from the babies, the children,

and the mothers, and we looked to see when these bacteria are

acquired.

This is a super busy slide, but what I'd like you to look

at is the fact that the first column, the bacteria that they

acquired in the first column, are carried throughout life. So

your bacteria accumulate in your body long before your teeth

come in, so even without teeth, those bacteria are there and

they stay, they are there to stay. A second set of bacteria

are acquired when you get teeth, and those bacteria keep

staying on, too. So, basically, within the mouth, bacteria

come in very early, and they are there to stay, and they are

your friends. So we need our biofilms.

We know that smoking increases the risk for cancer or cavities and peritonitis or gum disease. So the odds ratio for oral cancer is about 18-fold in a smoker; for cavities, it's about 10-fold; for peritonitis, it's anything from 16 to 20-fold depending on what type of gum disease you're looking at. And so, in my own practice -- I'm a periodontist. In my own practice, about half of my patients are smokers. So if I lost the smokers, I would lose half my practice. What we did was we said okay -- and we're talking about disease, but let's talk about when these bacteria can show changes.

Here you're looking at what's called a principal component analysis. Each of these dots is a sample. So here you are looking at 100 smokers and 100 nonsmokers or never smokers. What we're seeing, the closer the two dots, the more microbially similar they are. You can see that the smokers are clustering in a group by themselves, and the nonsmokers are kind of spread out through the bottom half. The most important thing to remember here is that none of these people have clinical disease. They are absolutely healthy people -- people, you know, who, like you and me, would go to their hygienist and dentist, and they would say okay, we'll see you next year, everything's looking great, and they'll give you a

lollipop if you're a child. But that's the kind of people

these are. And so what we found was not just are these

communities different, but in smokers these communities are

highly pathogen-rich, and they're not just oral pathogens.

They are systemic pathogens. Many of them are respiratory

pathogens. So it's almost as if the oral community in smokers

is a reservoir for respiratory pathogens.

     And so that kind of dust, the whole thing is one

geographically connected to it, and so it's possible that, you

know, a lot of these bacteria move from location to location,

and so which brings us to the point. Can your oral bacteria,

since these oral bacteria -- and this is -- I just showed you

the smokers. We've done this with obesity, and we've done this

with diabetes, we've done this with a lot of things. Before

the clinical onset of disease, these bacteria have changed. So

even in clinically healthy -- people with no gum disease,

people with no cancer, no cavities, just because they have

diabetes, just because they smoke, just because they're obese,

these bacteria, however, are already showing shifts. And so

the question we ask is, can these oral bacteria be the canary

in the coal mine? Can they be warning signals? Since they

respond so quickly to changes in the oral environment, can they

be the canary in the coal mine? Can they be warning you that

something is bound to happen downstream?

And so we believe that that is a possibility, and based on

that hypothesis, we did two studies. We said okay, let's look

at electronic cigarettes. We've all heard of the different

components of electronic cigarettes. We've also heard that,

you know, the main difference between electronic cigarettes and

smoke seems to be the tar component. So here you're looking at

-- you know, we took cigarette smoke, and we removed each of

these components. We removed the heavy metal component, we

removed the nicotine component, and we removed the tar, and we

asked how each of these affect the gene expression within

bacterial communities, because these are the communities that

are found in your mouth. And what we found was -- so

basically, we did what's called RNA seq, which is looking at

the transcripts, the gene, the coding information that is

produced by these bacteria in response to any environment. And

what we found was -- so forget the outer circle guys. That's

clearly not important even though it looks so big; it's really

not important. What we should be focusing on are the red and

the green bars on the inner side. And if you look at it, you

can see that -- so if smoke and control, smoke and non-

controlled biofilms were identical, the green and the red bar

should be 50/50. You can clearly see that as soon as you add

smoke to this environment, there is a huge shift in gene

expression. So smoke changes gene expression within biofilms

when compared to non-smoke controls. Sure.

So we said, okay, let's compare smoke to heavy metals; how

much do heavy metals resemble cigarette smoke? And we found

that heavy metals do resemble cigarette smoke for a lot -- you

can see a lot of the red and green bars are 50/50 at this

point, but there are some critical differences and especially

in response to stress, heat shock proteins, adhesion,

virulence, drug resistance, clustering, different bacterial

gene expressions, all of which are important for survival of

these organisms in any environment. So there are critical

differences between smoke and heavy metals, whole smoke and

heavy metals, which is not really surprising.

Then we asked about smoke and tar, and you can see most of

the bars and inner circle bars are 50/50, so smoke and tar seem

to be very similar; however, there do seem to be certain

critical responses, changes especially with response to iron

acquisition, fatty acid synthesis, adhesion. How sticky are

these biofilms? How difficult is it for you to brush them off,

to scrub them off? Can they cause cavities, can they stick on there? So important things like that.

And then we came to smoking and nicotine, and we found that there were very, very few differences between smoke and nicotine. You can see that for the most part, most of these bars are halfway, you know, filled in each of these. So this was an in vitro experiment, and so when we quantified these differences, we found that about half of the effects of cigarette smoke, whole smoke, could be seen with nicotine alone. About two -- of 25% of the effects of cigarette smoke could be seen with heavy metals, and with tar there was about another 25%. So, essentially, that's how it's split out, you know, 2:1:1, where the different effects that could be attributable to the composite, the whole smoke, when you compare them to nicotine, heavy metals, and tar.

Then we move to an in vivo experiment where we looked to see the effects of e-cigarettes on the oral environment. This is started, this is funded by Center for Tobacco Excellence at Ohio State. I'm only going to show you a part of the data because we're not completely through this. So let's walk you through this.

I have five groups here. I'm going to show you data from

the first three groups; the last two groups are incomplete. We

have 25 cigarette smokers, 25 never smokers, 25 high END --

high nicotine ENDS, and then nicotine-free ENDS, and of course,

cigarette smokers dual users. So the definitions are current

smokers, a 5-pack year or more smoker who is currently smoking;

and never smokers, a CDC guideline, less than 100 cigarettes in

a lifetime, not smoking; high ENDS e-cigarettes, this is what

we used, 13 to 16 mg cartridges four times a day or an

equivalent of that; and then dual use is, you know, pretty much

all-comers, former cigarette smokers who are now e-cigarettes

or people who are smoking both cigarettes as well as

e-cigarettes.

So essentially you had to be youngish, 18 to 40. You had

to have at least 20 teeth in your dentition. I mean, we were

really not looking for people -- one of the biggest reasons,

you know, we didn't look for people with -- smoking causes a

lot of tooth loss, so there's no point in looking at someone,

you know, who's past where we can help them, and so we were

looking for all of these things. And, of course, we're looking

at bacteria, so we didn't want people who have been treated

with antibiotics, you know, or professional cleaning. And so

all of these different factors. And essentially we found, you

know, the population of Ohio State, tweeting works

fantastically. These kids will come when you tweet. So we

used flyers and Facebook advertisements, and we do all of these

different things.

So I'm going to go and tell you what we did. So we looked

at the whole genome, the whole bacterial genome, what are the

different genes. Last time I showed you, I showed you the

different transcripts. Now we're looking -- we're taking a

step back and looking at the codes that, you know, make those

transcripts. So this is one step behind the gene expression

data that I showed you. And what we really found -- and I'm

just going to put this one slide up for now. These are your

three groups. So basically you are looking at non-smokers in

green, smokers in red, and e-cig users in a kind of tan-yellowy

color, so basically this is the functional potential. So this

is all the bacterial genes that are present in the oral

microbiome of smokers and nonsmokers. So the first slide tells

you that nonsmokers are significantly different from smokers,

that many genes. So we had about 6,000 bacterial genes; 3,000

of them, half, were different between smokers and nonsmokers,

and that comes as no surprise to anyone in this room. We've

always known that.

The bigger surprise to us was that nonsmokers were about different in 2,000 genes from e-cigarette users. So e-cigarettes do change the microbiome, and these are not former smokers; these are pure just e-cigarette users who started off by using e-cigarettes. And so we said, okay, let's make a third comparison of e-cigarettes and smokers, and you can see that very, very few genes are different between e-cigarette users and nonsmokers [sic]. Yes, they are significant; there are about 800 genes that are different between e-cigarettes and smokers, but the differences seem to be narrowing. So cigarettes and no cigarettes are clearly different; cigarettes -- no cigarettes and e-cigarettes are very different; and smoking and e-cigarettes kind of start coming a little, little closer than I would be comfortable with.

So, basically, the summary is that the oral microbiome responds to environmental changes long before the host does, and so we ask if it could be used as a risk indicator. Smoking causes pathogen enrichment in the oral microbiome, and there is oodles of evidence out there to show that this predisposes this environment for disease. What we're finding is that through these two small-scale studies, e-cigarettes do seem to cause similar changes in both communities, composition, as well as

bacterial gene expression, which leads us to ask is the harm from e-cigarettes similar to smoking?

So I'd like to acknowledge my mentors, Peter Shields and Mary Ellen Wewers, and of course, my lab folks who have been working on all of this stuff.

(Applause.)

DR. DRESLER: Thank you.

Remember the clarifying questions which will be coming up after this next speaker, so get your cards ready and pass it out.

And -- oh, can I make sure that this pointer is working? I can't see it. There, voila. Now where did it go? I don't seem to have control over it. I see it, but I don't have control. Okay, and -- let's see if we can get that fixed.

Oh, it has to be on.

UNIDENTIFIED SPEAKER: There we go.

DR. DRESLER: Who knew to turn it on? Okay, thank you very much.

Okay, our next speaker is Dr. William Bailey from the University of Alabama at Birmingham speaking on the Possible Health Effects of E-Cigarettes.

You now have a pointer that works.

DR. BAILEY: What's that?

DR. DRESLER: You have a pointer that works.

(Off microphone comment.)

DR. DRESLER: No, sir. No.

DR. BAILEY: Point at that?

DR. DRESLER: Well, yeah. So it is this --

DR. BAILEY: Okay.

DR. DRESLER: -- mouse thing that now moves readily when you want it, okay?

DR. BAILEY: Oh, excellent. Okay.

DR. DRESLER: Okay.

DR. BAILEY: Thank you.

Now, this really should be titled Possible Lung Health Effects or Pulmonary Health Effects, and that was my fault. I just called it this because I always think everything's related to the lungs, since I'm a pulmonologist. But that's really not fair.

Now, I'm going to try to develop a theme, and the next eight slides are part of a continuum for that theme to be developed, if it works, and so those who would be interested in the theme, it would be helpful to pay attention to each of the next eight slides because they do go together.

Now, this is a diagram done by Dr. Fletcher a number of

years ago in the '70s when he predicted that you could really

change the decline of lung function in smokers who have that

based on getting them to quit smoking. Now, if you look at the

top red line, that's normal people who don't smoke or those

people who, for whatever genetic reason, are protected from

developing COPD and don't decline their lung function. And

we're not really sure what percentage decline, but many people

say 20%; it's really at least 40%. And the reason it's at

least 40% and others say 20% is because at least half die on

the way to end stage lung disease. Now, COPD is emphysema and

chronic bronchitis.

Now, as you can see -- let's see how this pointer works.

Yeah. This is really poorly -- well, where did it go?

Am I changing this with the pointer? No.

See that yellow line is very faint, I'm sure. That's

where somebody quits about age 40, and you can really do some

good with that. They live longer, but they don't get

disability until quite some time later. It's better to never

smoke. But what we were doing at that time is getting people

to quit smoking when they began to be symptomatic, come to the

hospital for the first time; that's when they had really very

severe disease. And you see they just lengthened their period

of disability, not necessarily the best thing.

Now, when we did a big study, the Lung Health Study, to

determine could we really affect this, and this was really in

the '80s and we didn't know -- we knew smoking was bad,

everybody knew that, but we didn't really know if we could get

people to quit smoking, we could have an impact on the decline

of lung function. And it's very clear that we could. The top

line is sustained quitters. In that study they stopped and

never started again, compared to those that are continuing

smokers. Now, the sustained quitters did even better than

Dr. Fletcher predicted. They went up for a while and then only

gradually declined, and they didn't decline just with age

alone. Now, remember that and we're going to talk here about

e-cigarette users. Now, this is, as all of our studies with

e-cigarettes, not a definitive study, it's not a control

clinical trial, but it is an interesting natural history of

e-cigarette use and of other things as well.

Now, what this is based on is we had funding for a

controlled clinical trial of use of an internet-based

intervention, a very inexpensive intervention, and we decided,

with some additional funding -- all this was from NIDA -- to

see what happened to e-cigarettes during this study. And these

people were the ones in the control, so we would not have any

impact of the intervention. And we looked to see what were

they doing when they quit smoking, if they quit smoking. Now,

you got to remember, smoking cessation is a confluence of

facts. A lot of things come together, and you can't just blame

your treatment. Sometimes also the patient just was told they

had ischemic heart disease and they're motivated from that

standpoint. Sometimes it was just, just had a baby, and

they're motivated from that standpoint. So all of the benefits

are not just from the drug itself, if it's a drug.

Well, what was interesting is the vast majority of these

patients, 364, quit cold turkey, used no medication. Thank

you. Those -- about 84 used a quit aid, and 31% quit smoking;

36% cold turkey; quit aid plus e-cigarettes less than that,

25%; and then e-cigarette alone, 20%. Now, another thing about

these figures is, we did cotinine validation, chemical

validation, and about half of these people were not able to be

validated as really quitting smoking, so you could reduce those

numbers by half if you looked at it from that standpoint. This

is self-report.

I see, I'm pushing this. That's the one?

DR. DRESLER: It should be.

DR. BAILEY: Oh, okay.

Now, the question is, again, in this natural history of these people who were smokers to begin with and how many turned out to be dual users, and this was at 6 months after hospitalization. Well, 90% at 6 months, 87% at 12 months. And so most people who use e-cigarettes, if they're smokers, are dual users. But taking these dual users, again -- yeah, okay. The question comes up, what about harm reduction? Are these people really reducing their cigarette consumption? And this one looks at how many days in a month they smoke. And both e-cigarettes and no e-cigarettes reduced it, but a little bit more in terms of average days for the e-cigarettes. But if you look at the median and mode, not just the mean, you see that, in fact, most of the people were smoking every day, and there were some people that were smoking very few days to give you the mean.

Now, the same thing for cigarettes, the number of cigarettes. E-cigarettes reduced the number of cigarettes from 10 -- from 12.3 to 10, and that seemed to be consistent across the board. But there still were people who smoke 50 or 60 cigarettes a day.

Now, this is 11 years later or 11 years after the beginning of the Lung Health Study, and a follow-up that we did -- and you see the sustained quitters maintain a very much less rapid decline of their pulmonary function. The continuous smokers maintain their inexorable and severe decline, but the intermittent smokers, which we were hoping to see as harm reduction, they were very close to the continuous smokers. Now, based on the limited data that we had before, it looks like e-cigarette smokers that start out as smokers become intermittent quitters based on that data.

Now, what about asthma? That's the other big disease that we would think e-cigarettes might have an impact. Well, there are articles and stories about theatrical fog, theatrical fog they use for these scenes, propylene glycol was used for years, but it was stopped because it caused cough for some people. So they use dry ice primarily now. Another article in -- and there was an article in the literature; if anybody wants to see it, I'll be glad to give it to them afterwards. Another study -- and, again, all of these I have the reference for -- single exposure of e-cigarette produced some slight changes in airway resistance and FeNO. Slight changes; may not be important. But they were kind of tending towards an asthmatic change.

There was a user blog of e-cigarette users, and it's amazing

the number of blogs there are that talk about e-cigarettes and

they talk to each other. Vapers are -- it's almost a

community, I would guess. And they're looking out for each

other, and they say that -- this particular blog said be

careful of propylene glycol because 1 out of 10 smokers or

vapers are going to be sensitive to that. Well, that's

consistent with propylene glycol up through -- with the

theatrical fog, and so that's an interesting point. And then

there was a scientific article that sort of averaged all these

blogs, I mean -- yeah. And brought together symptoms that were

reported by vapers, and basically cough and throat irritation

were, by far, the two most common.

     Now, everybody's talked about what's in e-juice and in the

e-cigarette vapor and so forth, and so I won't belabor that,

but one of the -- this is just the e-juice. And you see

there's a huge variation in terms of what all is in each

product, and that's one of our problems, is to really study

this consistently. We got to have a single consistent product

that we could really compare, and nobody has yet. Now, we do

know, though, in general, the solution has nicotine, either

propylene glycol or glycerin or both, a combination. We heard

that propylene glycol might be an irritant and cause problems

with asthma. Might be; we don't know yet. Glycerin clearly is

a product that, when heated, will produce acrolein. Now,

acrolein, in addition to cardiovascular effects also, we

believe, is a real serious lung disease problem. We don't know

if a concentration of this is significant or not, but we need

to study it. Now, when you go to the vapor, you do get the

additional components of acrolein, formaldehyde, and

acetaldehyde most of the time. Now, in some of the products

that we've looked at, it doesn't always occur, and I'm not sure

why that is. But, again, that all needs to be worked out.

Now, I'm going to show you some mice, bronchoalveolar

lavage, which means we washed out the airways and examined the

cells that were in the airways. What we did is we exposed

these mice for what would be equivalent of about one-third of a

puff, a human puff, of an e-cigarette or whatever else we used.

And they were given that one exposure, and then 24 hours later,

to give them a chance to have inflammatory response, we did the

bronchoalveolar lavage. And as you can see here, on the first

panel, the first upper right-hand panel, this was buffered

saline, phosphate-buffered saline control, and you got mostly

macrophage; it's not anything else, which is normal. Then if

we did the next one down, B, which is the left-hand lower, we

used a reference cigarette, a cigarette that is standardized

and is used for research purposes, and you see you're beginning

to get neutrophils and some activated macrophages. I'm going

to show the specifics of what they are in just a minute, so --

because I know you all can't count the cells and so forth.

Then C, the upper right-hand quadrant, we have a combination of

propylene glycol and vegetable glycerin. And there we also

have activated macrophages; those are the ones that will begin

to secrete various cytokines. We have, in this area here, the

large cells right there, that's denuded epithelium, and then we

have polys or neutrophils. That's 50/50 propylene glycol and

glycerin at 3.5 volts. We jumped it up to 4.8 volts, which is

still consistent with some of the commercial products off the

shelf, and you had about the same thing, it looks like.

Now, this is Johnson Creek tobacco flavored, and this is

-- this comes in a bottle to be refilled for the different

cartridges, and this was Johnson Creek at 3.3 and then the

lower one is 4.8. No flavorings other than tobacco flavor.

And you see you get some of the same thing, activated

macrophages. You can see these macrophages that are having

little pods sticking out, and they're going to be secreting

things, and you see polys around. And then the same thing when

you do it at 4.8. And then over here, this is the Metro brand

disposable, and that's just one of the cigarettes we bought.

We were doing some studies about advertising, where these

products were, all that kind of stuff, and so in the process,

we just bought some of them, and this is one that we bought.

We don't know what the battery strength is because we couldn't

take it out. We tore it up every time we tried to get to the

battery. But, nevertheless, it was an off-the-shelf and used

product.

     And you see in the bottom that the black bar are

macrophages, and all of the rest of them we're going to look at

a little bit better are polys and activated macrophages, which

is -- this is a better picture of that. Well, the control, you

didn't really get many polys or activated macrophages. The

first one we go across. With the cigarette you did, and with

the propylene glycol and vegetable glycerin, you got a little

bit more, but I wouldn't -- it was statistically significant,

but this is small numbers, so we don't want to pay too much

attention to it. And then, as we go up with the higher

voltage, it is higher. If we look at the Johnson Creek tobacco

flavored, two voltage, they were about the same. But then if

we went up to the Metro cigarette, without knowing really what

all is in that, it was the highest. But that, I think that

does show you that there is inflammation in mice, I don't think

there's any question about that, within 24 hours from them

smoking a small amount of an e-cigarette. Now, that doesn't

say it's inflammation in man, and we got to do many other

studies, but it's the beginning of things, and we do it this

way, and sometimes things that happen in mice don't happen in

man. I wouldn't say we've got any definitive information here,

but we've got to look at it, no question about it.

And with that, I will stop. I've got -- be glad to -- and

we're going to answer questions later, correct? Thank you.

(Applause.)

DR. DRESLER: Thank you.

Okay, clarifying questions.

Dr. Kumar, okay. Does preliminary data in your study show

any difference between nicotine and non-nicotine e-cigarettes

on bacteria? Was propylene glycol-based liquid used for your

study?

So any difference between nicotine and non-nicotine

e-cigarettes on bacteria?

DR. KUMAR: So, yes, we did not. That's what I was trying

to say. We have not done the non-nicotine e-cigarette groups

yet. So the three out of the five groups that I showed you,

one was current smokers, one was never smokers, one was high

END -- you know, high-dose ENDS, one was no nicotine ENDS, and

then -- so the no nicotine and the dual users groups are not

completed yet, so I don't have data on that just yet.

DR. DRESLER: Okay. Well, don't sit down because I have a

lot for you, okay?

Was propylene glycol-based liquid used in your study?

DR. KUMAR: No.

DR. DRESLER: Okay.

You appear to have established a correlation between oral

nicotine use and good bacteria depletion. Shouldn't Nicotrol

users be very worried?

DR. KUMAR: Yes. So there's a whole R01 that's funded on,

you know, looking at other doses of nicotine, other modes of

nicotine delivery, nicotine lozenges. You know, gum, all of

that. And we're finding that those changes with the non-

vaporized or the non-aerosol forms of nicotine don't seem to be

as dramatic on oral bacteria as, you know, smoke -- or nicotine

from smoke or nicotine from electronic cigarettes. Why? I

don't know. And the same thing, it's not just us. Many others

have shown that chewing tobacco, snuff, you know, snus, all of those things don't seem to have the same effect on oral bacteria or on oral health as combustion tobacco does, so there is a huge difference between those two types of delivery.

DR. DRESLER: So what is the causal link between nicotine and good bacterial depletion?

DR. KUMAR: Okay, so -- and here's -- we're just getting ready to put this together, so -- and, again, this is an in vitro experiment that we did. So when you think of the bacteria, they're not living by themselves. This is not pond water they're living in. They're living in your oral cavity, you know, sitting right next to your mucosal, and your body is controlling them. Your body decides. I mean, you eat, drink, do multiple things all day long. Multiple bacteria, the whole world and his brother passes through your mouth. Not everything sticks there, you know, only few bacteria stick. So there's a reason why certain bacteria stick. And we've done some work showing that your genotype, your gender, your ethnicity, your genetics have a huge role in deciding in what bacteria will stay in your mouth. And so based on all of that, there is an interaction between the host and the bacteria constantly. Your body is looking at this microbiome and

saying, yes, I'll leave you here, or no, move out of the way.

You know, it's constantly happening. There's this cross-talk.

And so we started looking at the elements of this cross-talk

and how smoking or e-cigarettes or nicotine can change this

cross-talk pattern.

So what we found was, first thing, that smoking shuts down

transcription within the good bacteria, so these bacteria lose

their basic survival mechanisms, oxidative phosphorylation,

adhesion, stress responses. Shuts down. And so then, the

other -- you know, good bacteria are good only because your

body sees them as good. They don't label themselves as good

bacteria. Your body calls them good because it tolerates them,

it's willing to live with them. So that's what we should

understand about good bacteria; it's us who determine what the

good bacteria are. And so suddenly these bacteria throw out

all of these gene expression patterns that are completely

foreign to the body, and so the epithelial cell response

immediately, immediately within 2 hours of seeing a smoke

condition, good bacterial biofilm, the host response spikes.

It goes through the roof. There is a 4,000-fold increase in

IL-8. There is a 200-fold increase in reactive oxygen species

within these cells. So your body goes nuts seeing these good

bacteria that have now been smoke conditioned, and within 4

hours this whole commensal biofilm is dead; 60% of the bacteria

within this commensal biofilm just die out. And so we think

that that clears the real estate. Think about it.

Your commensal biofilm is your lawn; it's keeping things

there and, you know, they die out, and so it clears the real

estate, and every other person and his brother seems to come in

and colonize. There're multiple mechanisms, multiple different

stories, but we're just scratching the surface of all of this

to see what it is that's going on, so if that even begins to

answer the question that I was asked -- it's very complex, I

guess.

DR. DRESLER: Does it change after cessation? So do you

see it go back to baseline when you quit e-cigarettes, and do

you see it go back to baseline after you quit cigarettes?

DR. KUMAR: Super. So we've not done the e-cigarette

study. The little amount of money we got from these folks,

first -- no, I don't mean that they gave us a little money. I

said the only money we got was, you know, from them so far to

study it, so we don't know about e-cigarettes. But I will tell

you the good news with smoking cessation is within 3 months of

smoking cessation, your microbiome returns to health. So we

have an R01 that's studying smoking cessation right now. We

have a publication in 2009 that looked at a 12-year -- you

know, 12-month smoking cessation and bacterial change. We

found that within 3 months, substantial changes, noticeable

enough to be statistically significant in a group of n=11 per

group, so it was still relevant in that group, and so now we're

doing a very large-scale study, and we're finding that within

3 months this community completely shifts. So smoking

cessation works, folks.

DR. DRESLER: Okay, let's do one more.

What sort of e-cig volume dose gene response did you

notice? So did you test a volume dose gene response?

DR. KUMAR: Okay. So, yes, we did. We did. And both

with -- and like I said. So this is an in vitro study, so in

that model there was really no dose response. It was an all or

none response. So we did different doses. We started with,

you know, whatever would be the equivalent of the high dose

ENDS and the medium dose ENDS and the low dose ENDS. We really

did not find -- as soon as these people saw, as soon as this --

and when I say people, I mean the microbial community, the

bacteria. As soon as these bacteria saw, you know, the

components from these things, they just shut down. They simply

just shut down, so -- and we, you know, tried it with multiple

different things. Like I said, we tried it with just pure

nicotine alone; we did, you know, cigarette smoke, extract the

whole smoke; we removed the metal, heavy metals, from cigarette

smoke using cytosine; we removed tar; we did multiple different

experiments. In all of these, it was an all or none, so it

didn't matter how much or how little smoke or nicotine or e-cig

these bacteria saw, as soon as they saw something, they just

shut off transcription.

DR. DRESLER: How about a very short answer? How do you

measure gene expression? A short.

DR. KUMAR: Oh, my goodness. Okay, we measure gene

expression by RNA seq.

Thank you, no.

(Laughter.)

DR. KUMAR: So gene expression is a very complex measure,

and I showed you the whole process, so really take out the mRNA

that comes out of the community. You take all the RNA, you

remove all the other small RNAs, you take the messenger RNA,

you run it through a sequencer. It spits out all of these

sequences. And then you look for genes that are super

different between groups, and then you do what's called real

time PCR or reverse transcripted PCR for some of these targets,
and then you validate them and see if it is real or if it's
just a sequencing artifact. And then you go back and you take
the supernatant, and you do a lyzer to see if the protein of
the gene expression actually matches the protein.

Pure genes are constantly being expressed, and your body
decides oh, that was a wrong message, I didn't want that
protein really expressed, and so it shuts down. From
expression to protein formation, there is another step that,
you know, in which that can be shut down. So the ultimate
validation is the protein that's formed. It's that, there. So
then you go back and you measure the protein that could have --
you know, the target protein that could have been measured.
So, yes, there's several different steps to going back to gene
expression.

DR. DRESLER: All right. So there's no -- it's not a
short process in doing gene expression. I think that's a fair
statement. And expensive. Yes, it is.

Dr. Bailey, do the mice in the study get rest from
exposure?

DR. BAILEY: I'm sorry, what's that? Rest?

DR. DRESLER: Yes. So are you running those -- what are

you doing with the mice? Are they just getting rest after --

DR. BAILEY: Yeah, sure. No, they just have the 20

minutes of inhaling the equivalent of one-third of a puff of

whatever substance, and we had those seven different things.

And then after that, they just go back into their cage and wait

until the next day, and 24 hours later we do the BAL. Put a

little tube down there, wash it out, bring it out, and then

quantify per cubic milliliter about how many cells there are,

and that's what we report. We got -- the same thing is true

whether you do percentage of cells or number of cells in terms

of the order.

DR. DRESLER: Great. All right, thank you. And we will

have a panel this afternoon and more questions and answers.

It is now break time. Thank you for going through that

little bit longer session. Fifteen minute break, so let's

start again at 25 till.

Thank you.

(Off the record at 10:22 a.m.)

(On the record at 10:37 a.m.)

DR. DRESLER: Okay, we're going to move on to the next set

of speakers, and the first one is Dr. Cheryl Oncken, who is

speaking on Potential Risks and Benefits of Electronic

Cigarette Use During Pregnancy.

DR. ONCKEN: Thank you for the invitation to speak. I'll be talking about the potential risks and benefits of electronic cigarette use during pregnancy.

Before I begin, I'd like to list my disclosures, primarily NIH funding and also FDA funding. In one of my R01-funded grants, I received free nicotine and placebo inhaler for smoking cessation for that study, and I've also had previous pharmaceutical support.

As many of you know, electronic cigarette use is increasing in women of reproductive age. And some surveys suggest that electronic cigarette use is perceived to be less harmful than cigarette smoking during pregnancy. And together these data suggest that electronic cigarette use may be increasing in pregnant women, although I don't have any data on that.

But what I did find is one case report. In this particular article, there was a 22-year-old pregnant woman who smoked about 10 cigarettes a day before pregnancy. When she learned that she was pregnant, she purchased a rechargeable electronic cigarette device over the Internet. Her intention was to quit, but was able to reduce smoking to 3 cigarettes a

day. And her rationale for use was that electronic cigarettes may not be as bad for her health, it may be easier to help her cut down or quit, they taste better, and are fashionable. So a lot of reasons for this person to use is similar to what was discussed yesterday, in that many people may be using these to quit smoking and to improve their health, and that may be true in pregnant women as well.

So the purpose of this talk, first of all, I'll review nicotine replacement trials that have been conducted for smoking cessation during pregnancy, and the rationale for that is that it may have some insight into the potential risks and benefits for electronic cigarettes. I'll discuss theoretical potential risks and benefits of electronic cigarette use during pregnancy and discuss potential avenues for future research.

So what have we learned about NRT trials and pregnancy? There's been two types of studies that have been conducted, and the main purpose of these studies have been to help pregnant women quit smoking. One group of studies is called effectiveness studies, and these are randomized but not placebo-controlled studies, looking at this as an aid to cessation, and women are knowing what they are taking. Efficacy studies are what we call placebo-controlled trials.

Everybody is getting a medication, they don't necessarily know what they're on, and they're followed for smoking cessation and outcomes. What we have learned is that in some trials, particularly the efficacy trials, which are considered the gold standard, is that birth weight and gestational age may be sensitive markers for a potential benefit of nicotine replacement therapy.

These are the effectiveness studies, and what you can see is three different trials, different agents, that they have helped potentially increase quit rates relative to control in all these trials.

Efficacy studies which are placebo-controlled trials, in contrast, have not shown a significant increase in helping quit rates, but what they have found is that there has been a higher birth weight in the nicotine versus the placebo group in two studies, and the potential rationale for that is reduction in toxins of other components of tobacco smoke. Actually, I should mention in our trial, we actually found in our nicotine group an overall reduction in nicotine exposure, which may have had an additional benefit. But the one issue that we've seen in efficacy trials is that we have not really improved quit rates, which is the goal.

So one potential benefit of electronic cigarettes may be to increase quit rates. There are some sensory aspects with using electronic cigarettes, and from the literature, we know that women may be especially sensitive to some of the sensory aspects of smoking. Another potential benefit of electronic cigarettes is that they have a no nicotine option, which would be potentially beneficial because we know nicotine is potentially harmful during pregnancy. One of the major potential benefits of electronic cigarettes is that they reduce or eliminate carbon monoxide exposure, which is a major reproductive toxin. In animal studies it has been linked to low birth weight and neurotoxicity. And it has been mentioned previously, studies have shown that there's a lot of evidence that some electronic cigarettes reduce exposure to not only nicotine, but also carcinogens and some of the other toxicants found in tobacco smoke.

So what could be some of the potential risks of electronic cigarettes during pregnancy? There's a lot of data to suggest that many users are dual users, and that may not reduce overall nicotine and toxicant exposure; and some studies suggest it actually could potentially undermine cessation. One of the things that are in some electronic cigarettes but not in

regular cigarettes are some of the flavors. There's been

studies showing, looking at the impact of flavors on

cytotoxicity to embryonic stem cells, mouse neuro stem cells,

and human pulmonary fibroblasts. And, in general, for most

flavors, human embryonic stem cells were more sensitive for

cell death than adult fibroblasts. Some flavors had more

cytotoxicity than others, such as cinnamon, and a follow-up

study confirmed this. Whether this is relevant to humans and

clinically is not known, but because of this finding, it should

be further evaluated.

We know from our last talk that propylene glycol could

potentially be an irritant, which could be a concern

potentially for pregnant asthmatics. There is one study

recently -- although most studies show a decreased formaldehyde

exposure, one study in the laboratory setting raised the

possibility for increased exposure, and the reason why that may

be potentially important for pregnant women is that

formaldehyde has been associated with reproductive toxicity,

mainly in epidemiologic studies such as women that have been

exposed at work, like textile workers. There's been some

evidence for increased risk of miscarriage and all other

adverse outcomes. Although rare, some -- there's been some

reports of contaminants in some of the refill fluids, which would potentially be a problem for pregnancy. And then there's always what we don't know and potential unknown risks.

So research needs. Although there's a lot of studies on epidemiology of, for example, teenagers using electronic cigarettes and other populations, I could not find really any during pregnancy, so I think that's a need, trying to determine the prevalence, what products people are using, you know, what are their overall levels of exposure to nicotine and other toxicants, and are they helping women quit smoking. I think basic science and animal studies are needed, and potentially in the areas of flavors as well, looking at cytotoxic, genotoxic, reproductive and developmental toxicity.

Pharmacokinetics, potentially recruiting women that are already using electronic cigarettes, trying to determine what are the levels of nicotine exposure, what are the acute levels of nicotine exposure when using, because that's had some implications on maternal and fetal dynamics, and potentially clinical trials after appropriate product standardization and safety testing and a clear pattern of benefit in non-pregnant smokers.

So, in summary, electronic cigarette use may be increasing

in pregnant women. A need exists to better determine the risk

and benefit profile in this population. And regulatory actions

regarding electronic cigarettes should consider the potential

reproductive toxicity of these products.

With that, I'm finished.

(Applause.)

DR. DRESLER: Okay. Thank you, Dr. Oncken.

Our next speaker is Dr. Suter from the Baylor College of

Medicine, Electronic Cigarette Use in Pregnancy: Potential

Effects on Fetal Health and Development.

DR. SUTER: Thank you very much to the organizers for the

invitation to speak today. I have no conflicts of interest to

report.

So who is using e-cigarettes? We know, from a major

survey from the CDC, the tobacco use survey, that middle and

high school students are using them and that the amount of

students who have tried them doubled from 2011 to 2012. And we

have reason to believe these trends are continuing. It has

been reported that women are significantly more likely to have

tried e-cigarettes than men, and we know that they're popular

amongst current and former smokers. But what we don't know and

what are important questions from a public health standpoint

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are: How does long-term exposure to nicotine affect fertility

in these students? How many pregnant women currently use

e-cigarettes? And will current smokers who become pregnant

turn to e-cigarettes as a smoking cessation device?

So in order for us to understand how pregnant women

perceive the risks of e-cigarette use in pregnancy to be, we've

conducted 11 focus groups with pregnant women for a total of 87

participants at three clinics in the greater Houston area, as

depicted on this map. From these focus groups, we were

interested to learn how these women perceived how e-cigarettes

compare to combustible tobacco cigarettes with regard to

safety, how they perceived the risk of e-cigarette use in

pregnancy to be, and we were curious to see if there's a stigma

of e-cigarette use in pregnancy.

So throughout the discussions with these women, we found

that they believed e-cigarettes are a safer and healthier

alternative to combustible tobacco cigarettes in non-pregnant

individuals, but they are not safe during pregnancy and are

likely harmful to the fetus; however, using e-cigarettes to

quit smoking may have fewer side effects than combustible

tobacco during pregnancy. And with regards to stigma, they

felt because there are fewer side effects of e-cigarettes, it

might not be as bad as smoking during pregnancy.

So not only do these pregnant women believe there are fewer risks and side effects, it also appears that their clinicians do as well. So these are the results of a survey from the American College of Obstetricians and Gynecologists, or ACOG. They screened current practicing OB/GYN clinicians, and they found that 40% of these clinicians don't regularly screen for non-combustible tobacco use, that 29% of these clinicians believe e-cigarettes are safer in pregnancy than combustible tobacco products, and that 14% of them believed e-cigarettes have no adverse health effects.

Now, given that we know that young women are using these devices, from our focus group studies and the ACOG survey, that their perception of risk of use in pregnancy is certainly less than that of combustible tobacco cigarettes, and the potential for a lack of a stigma, we do believe that e-cigarette use in pregnancy will quickly become an important public health issue. And, of course, when we consider this public health issue, we have to understand what are the health risks for the fetus with e-cigarette use.

Now, there aren't any studies on that specifically, but what we can do is look at the safety of the individual

components for the fetus. And of these individual components, there are actually quite a few studies on how nicotine affects fetal growth and development. So, first of all, of course we have to consider, when we're thinking about how nicotine affects the fetus, how it interacts with the placenta. We know from human and animal studies that nicotine readily crosses the placenta, and from studies in human and term placenta, that little to no nicotine metabolism occurs within the placenta itself. We know from animal studies that nicotine does alter placental development and function, and data from human studies shows that nicotine levels are actually higher in cord blood than maternal serum. Sampling of placenta, amniotic fluid, and fetal serum reveals higher nicotine concentrations in all of these samples compared to the maternal serum values. So, with that being said, if a mother does use an e-cigarette with nicotine, her fetus is going to immediately see that nicotine.

But what has been very important in our understanding about how nicotine affects fetal development is really looking at data from animal models that have given us insight into the effects of nicotine on the fetus. One of the most exciting -- some of the most exciting data has come from a non-human primate model of in-uterine nicotine exposure. This

was developed by Eliot Spindel and colleagues at the Oregon Health and Science University. So in these rhesus macaques, on Day 26 of pregnancy, the moms are either assigned to the control or the nicotine group, and they are administered either saline or 1 mg/kg of body weight per day of nicotine through an osmotic pump, subcutaneous osmotic pump, with this model system. They've looked at the development of the fetus, specifically gestational 134 of 166, which is comparable to Week 32 in humans, and they have looked at neonates, so full-term infants. From this model they found that in-uterine nicotine exposure significantly altered fetal lung structure. Specifically, they saw a reduction in internal surface area from the nicotine exposure in utero.

They found alterations in the fetal nicotinic acetylcholine receptor expression in distinct brain regions. They found an elevation of fetal brainstem serotonin levels and a deficit in cardiac norepinephrine levels. These are two things that are implicated in sudden infant death syndrome. In the neonate, they found decreased neonatal lung rate and volume. Now, interestingly, these are changes that are similar to those seen in neonates of smoking mothers, and they've also shown reduced neonatal plasma leptin levels.

Of interest in this non-human primate model, as they had noted, a lot of the damage from nicotine seemed to be occurring because of oxidative damage. Knowing that vitamin C is a powerful antioxidant, they actually supplemented some of these moms with a vitamin C supplementation, and they found that the vitamin C supplementation with the in utero nicotine exposure actually may worsen the effects of nicotine on the fetal brain; however, prevents the adverse effects of pulmonary function in neonates and ameliorates the elevation of serotonin levels and deficit in cardiac norepinephrine levels that were associated with sudden infant death syndrome. Of note, Dr. Spindel did take this to clinical trial where he -- pregnant women were supplemented with vitamin C, and it improved the newborn pulmonary function test. This was published last year in *JAMA*.

A lot more insight we got on how in utero nicotine exposure affects the fetus is through rat models of exposure. So there's two basic models. One, where the pregnant dam receives daily injections of nicotine, which is thought to mirror the spike in nicotine levels seen in smokers; however, daily injection is thought to cause stress to the animals, which might act as a confounding factor. Another model system is using the subcutaneous osmotic pump, which helps maintain a

steady state level of nicotine in the bloodstream; however, it's thought to be more similar to wearing a nicotine patch rather than the spikes seen from smoking.

From rat models of in utero exposure, it has been published that there are pulmonary consequences to the offspring, including alterations in lung development; metabolic consequences, including increased blood pressure, perivascular adipose tissue accumulation, and beta cell apoptosis; that there are neurological consequences, including serotonin transporter expression changes, changes in the cerebellum and hippocampus, as well as changes in nicotinic acetylcholine receptor in dopaminergic signaling. There are cognitive consequences including memory and learning deficits, and two studies did show that these offspring exposed in utero do show decreased fertility.

Very interesting, one researcher, Virender Rehan from UCLA, showed multi-generational effects of in utero exposure. So, in his model, they injected pregnant rats with either saline or nicotine starting at embryonic Day 6 all the way through postnatal Day 21, so that these offspring were exposed not just throughout gestation but lactation. And they found that in the F1 generation, their pulmonary function tests

revealed an asthma phenotype. What was interesting is that

these F1 generations were intercrossed, and they could follow

this asthma phenotype out to Generation 3. So, in other words,

even though the grandparents were the ones that were exposed in

utero to nicotine, the grandchildren did show signs of this

asthma phenotype. So these data that we've seen from animal

models certainly implicate that we want to continue studying

how nicotine affects fetal growth and development.

    When we look at the other individual components and their

effects on the fetus -- so propylene glycol, this is data that

was from the National Toxicity Program, Center for Evaluation

of Risks to Human Reproduction. So they summarized a lot of

the data on how this propylene glycol affects fertility and

reproduction. They reported on both rat and mouse models of

propylene glycol administration. Both had up to 1600 mg/kg of

body weight per day for 10 consecutive days of pregnancy, and

no studies showed a discernible dose effect for mother or

fetus, with the caveat that there were no long-term follow-up

studies on these offspring. As for the rest of the

ingredients, I did not find anything on how glycerin affects

fetal development, and as Drs. Drummond and Oncken have already

pointed out, for the flavorants, certainly the cinnamon flavor

has been shown to have cytotoxicity on embryonic stem cells; however, how that is going to translate into fetal health and development remains unknown.

So, in conclusion, we can see from these animal studies that no amount of nicotine is known to be safe in pregnancy; however, women who are smoking in pregnancy do have quite a bit of trouble quitting. We don't know what the effects of e-cigarettes without nicotine are on fetal development; however, given current trends, e-cigarette use in pregnancy is likely to become an imminent public health issue. So we believe future studies are needed, namely, animal model studies with maternal exposure to e-cigarette vapor. Of note, last month a study was published in *PLOS ONE* where they modified a cigarette smoke machine to expose rodents to e-cigarette vapor, so this would be very useful in studying how the vapor affects fertility and reproduction. And certainly we do need to follow women who are using e-cigarettes in pregnancy and record their outcomes.

With that, I'd like to thank my colleagues who helped us with the focus report, as well as Drs. Spindel and Rehan with whom we're studying the effects of nicotine on the fetus.

Thank you very much.

(Applause.)

DR. DRESLER: Thank you, Dr. Suter.

Our next speaker will be Dr. DiFranza from the University of Massachusetts Medical School speaking on Nicotine Addiction and E-cigarettes.

DR. DiFRANZA: And so I know, if you were here yesterday, you heard about nicotine addiction in adults. I'm going to talk about how it develops in adolescents and why that's a concern in regard to electronic cigarettes. Anybody who is addicted to nicotine, if they go too long without smoking, they're going to feel it, and they're going to feel withdrawal effects. And what we did was a study, because I had never smoked, to determine what does that feel like, what does it feel like when you need a cigarette. And we did focus groups with adults and adolescents, and what we found was that the first symptom of addiction to nicotine is that you just every once in a while, you want a cigarette, that's it. And it's like wanting some chocolate. It's mild, it's transient, it's easily ignored. You can put it out of your mind in a second and not think about it.

The next step in becoming addicted is when you develop a craving, so if you go too long without smoking, you'll crave a

cigarette. So what's that like? Well, people say, "I feel

like someone inside of me is really telling me to smoke." A

craving "just, like, pops in your head, like someone is sending

you a message." Craving is like "being hungry, but instead of

your stomach saying it, it's your brain...it's just hungry

except for a cigarette." So this is very different than you

feel like Mexican food tonight. Nobody in your head is telling

you it's time to eat Mexican food, so it's something

physiological going on.

And what we did was we put smokers and nonsmokers in our

fMRI magnet at the University of Massachusetts, and the smokers

were told not to smoke overnight. And that's all they did,

they just -- the smokers and nonsmokers lay inside the magnet,

and you look at their brain function, and we're interested in

the parts of the brain where -- that are associated with

addiction. And this is the insular cortex, and these are all

different slices in the nonsmokers, and it shows you how much

activity is going on in the insular cortex in nonsmokers. And

these are the same areas in smokers. You can see that the

brain just spontaneously lights up, and it feels like somebody

inside your head is telling you to smoke, and it is, your

insular cortex among other areas is lighting up, telling the

smoker it's time for a cigarette.

Craving is more intense than wanting, and it actually intrudes upon your thoughts. You might be doing your geometry homework, and all of a sudden the thought comes to your head, it's time for a cigarette.

Needing, the final stage of addiction, is it's "pretty urgent...you need it and you can't get your mind off of it." "You really want one. You know you need it. You know you'll feel normal after smoking, and you have to smoke to feel normal again," because the brain no longer functions normally without the presence of nicotine. And the craving, the wanting, and the needing is your brain's way of telling you that it needs nicotine in order to get back in balance.

So needing is an intense and urgent desire to smoke that's almost impossible to ignore. An individual must smoke to restore a normal mental or physical state. So when people are in this state, their reaction time is off, their concentration is off, they can't do anything as well as they do when they have their nicotine. And so an addiction develops. And this is true in adults and in adolescents, people go through these stages or levels where at first the only symptom they have of addiction is that every once in a while, maybe once a month,

they'll want a cigarette. And then the next stage is they
crave a cigarette, and then the next stage, final stage, is
needing a cigarette.

And this develops in the same sequence in all smokers and
in all chewing tobacco users and so forth, and that gave us the
idea that maybe there's something going on in the brain that's
developing the same sequence. Kind of if you're medically
trained, you know there's primary syphilis and secondary
syphilis and tertiary syphilis, and that a lot of disease,
especially infectious diseases, come in these stages, and so
these are the stages of addiction.

And we developed -- it's too small to see, but we
developed a three-question survey we put to smokers to see
which level they're in. And then we put them in the MRI
magnet, and we measure the density of neurons in different
parts of their brain, and we measure the activity of the
neurons in different parts of their brain, and we measure how
much the different parts of the brain talk to each other, and
we measure the number of nerve fibers connecting one part of
the brain to another. And we found where this X is, is where
the brains of smokers and nonsmokers differ most strongly in
the density of their neurons. And we found, as people went

from the wanting stage here, No. 1, to the craving stage,

No. 2, to the needing stage, No. 3, the number of fibers

connecting this part of the brain to the frontal cortex went

down from about 80 to probably about an average of 30.

So they lost over 50% of the nerve fibers connecting the

self-control part of the brain to the part of the brain that

generates the craving. So as you get more addicted, you have

less control. There's less neurological connections between

the reasoning part of your brain, up in the front here, to the

part of the brain that senses this wanting, craving, and

needing, and that's why it's so hard to quit smoking. So we

know the brain anatomy changes. How quickly does it change?

I'm going to skip this because we just showed that.

So how long does it take your brain to react to nicotine?

Well, a single dose of nicotine in animal studies stimulates a

cascade of neurotransmitters. It's not just nicotine, it's not

just dopamine; it's serotonin, norepinephrine, epinephrine, and

so forth. All these different neurochemicals are released, and

this initiates this remodeling in the brain, which we just

showed you in terms of the number of fibers and so forth in the

brain. And in animal studies, just giving one dose of nicotine

to a rat actually affects the function in the brain for at

least a month. It influences how much neurotransmitters are in

the brain, it affects their behavior for a month and so forth.

So just one dose.

And the initial dose of nicotine starts the process of

addiction. You're not fully addicted after one dose, of

course, but it starts this process; it starts this remodeling.

There's increased number of nicotine receptors in your brain.

In one study that was presented, SRNT showed an hour after a

single dose of nicotine to a nerve in a cell culture, increased

the number of dendrites, so nerve connections that were

growing. So 1 hour was all it took for that nerve to respond

to the nicotine and start to remodel itself. So each

additional dose, each additional cigarette advances the

addiction. And so -- let's see if this will work. It's

working.

So what this shows is in boys, we asked them do you have

craving for cigarettes. And this was done in Australia with

25,000 smokers.

I'm just trying to get -- there it is. Maybe not, okay.

So of the kids who had smoked one cigarette in their

lifetime, about 25% were saying they were already having

craving for nicotine. By the time we get to two cigarettes,

it's a little bit more; three to four, a little bit more; five
to nine cigarettes. By the time you get up to a full pack, 20
cigarettes here, more than half of the kids were at the second
stage of addiction. That's for the boys. And you'll see for
the girls, it took fewer cigarettes to get to the same point.
So the girls, by the time they smoked a pack of cigarettes, 10
to 20 cigarettes, 60% of them were already experiencing this
craving for nicotine.

So the concern with electronic cigarettes is how many
different flavors do you have to try to get addicted? So for
girls it may be as little as 5 to 10 flavors of different
cigarettes that you'd have to try before you're addicted. And
so there's one site, there -- I don't know how many flavors are
out, but there are lots of flavors and lots of kids curious
enough to try all the different flavors. They're going to be
addicted.

Let's just skip that.

So how heavily do you have to smoke? So most of these
surveys show that a lot of kids have tried e-cigarettes, but
they haven't gone on. So how many times would you have to try
an e-cigarette to get addicted? Well, this is based on
cigarettes, not e-cigarettes, but you can see that -- we see

loss of autonomy here. We're talking about exhaling

experiences, craving for nicotine. Among people, among

adolescents who are using tobacco less than once a month, about

a third to a half of them, boys, about a third of the boys and

half of the girls are already experiencing craving. By the

time they got up to using at least once a month, half of the

boys and almost three-quarters of the girls had experienced

craving. And you'll see that most addictions start before

daily smoking, so they're experimenting. Well, maybe an

e-cigarette here, a cigarette there, some chewing tobacco here

and there, and the exposure is built up and doesn't take too

many before you get addicted. So we're very concerned about

any products that are going to generate curiosity and be

fashionable for kids to try them. This is very different than

alcohol. You don't become an alcoholic after drinking five or

six beers. Alcoholism seems to build up over a long period of

time, as far as we understand. But for tobacco, it's the

opposite, as the neurological changes from nicotine are known,

in animal and cell cultures and so forth, to start with the

very first dose, and symptoms come on very quickly with very

low exposures.

So we still have 10 minutes now to go over my last slide,

and this is all the concerns specific to e-cigarettes. And so
let's start with number one. E-cigarettes are a concern
because they can initiate addiction in non-tobacco users. How
much? This is a problem; we don't know yet. We need a lot
more surveys. Just knowing that it could try one e-cigarette
isn't enough. We know about half of the kids who smoke one
cigarette out of curiosity never smoke a second cigarette. So
we need to know if this is true for e-cigarettes as well. We
don't know what percent of kids who would have started smoking
cigarettes start with an e-cigarette because that's the first
product available to them, so we don't really know how the
e-cigarettes are changing this dynamic of getting people
addicted. But we do know that they're generally perceived as
safer than cigarettes and probably because they are. But does
that perception of safety mean that kids are more likely to try
them? They don't think they're doing something that's so bad
if they're trying e-cigarettes.

Nobody in school has been telling them not to smoke
e-cigarettes. And when they talk about the perception of
safety, that never includes the perception of addiction,
because we did a survey, and 99% of the kids in the school said
cigarettes are addictive, but then we asked them would you get

addicted if you smoked them? Well, numbers are much lower,

maybe about 20% of kids thought they would get addicted if they

smoked an addictive product. So the perception that

e-cigarettes are safer probably also means that kids feel that

they're even less likely to get addicted to any cigarette.

The flavors are important because the flavor may make the

initial exposure more palatable. About half of kids who try

cigarettes never go on to another one because they taste so

bad, and despite the advertising, they all taste bad, and so

they have to have some social motivation usually to smoke the

second or third cigarette because it's not the pleasure and the

wonderful taste of the Marlboro that gets them to come back for

more. So flavoring that makes these products more palatable to

13-year-olds and 14-years olds, because that's the average age

of initiation of cigarette smoking, is a concern. It's a

marketing concern.

Now, one of the slides shown early this morning showed

that about 30% of e-cigarette users had experienced some

nausea. Well, that's what nicotine does to you; that's a side

effect. But that's what happens when you smoke your first

cigarette; you get nauseous because that's just a normal

reaction until you build up a tolerance.

Now, Marlboros and the cigarettes come in one strength pretty much. There's some difference in nicotine, but you can pretty much get the same amount of nicotine from all of them. But if you have e-cigarettes and they come with different gradations of nicotine concentration, you may find that the lower concentration is easier, it's more like a pediatric dose, that kids would be able to tolerate their first cigarette without getting nauseous and vomiting, getting dizzy and so forth. So that's a concern. And, of course, if -- nicotine itself is not completely innocuous. None of the drugs I prescribe as a physician are completely innocuous, and we wouldn't want to bring up a new generation of kids who are all addicted to nicotine; it does have effects. Addiction is not a good thing to have in your brain. And so the concern is that they may all become addicted. There's another wave. If the prevalence of e-cigarette use went up to 30 or 40% of high school students, that would certainly be a public health problem.

My biggest concern -- and this was hinted at by several of the other speakers, was that the prevalence of smoking in teenagers is the lowest it's been in any of our lifetimes. It's gone down by 75 to 80% over the last 10 or 15 years. But

why is that happening? Well, it's not because kids are more

convinced that cigarettes are dangerous. There are multiple

factors. One is they're too expensive. The kids who smoke

don't want to share them. They have cigarettes; instead of

giving them away to all their friends and getting them

addicted, they're hiding them. They're leaving their extra

cigarettes at home so they don't have to share them with their

classmates. So the price is a deterrent to kids smoking. The

fact that people can't smoke all around kids in the restaurants

and supermarkets and so forth has denormalized smoking. It's

not no longer seen as something that everybody smokes. So if

people start smoking e-cigarettes in restaurants and on

airplanes and shopping centers, it's going to renormalize

cigarette smoking, and that's a concern.

Kids can't easily buy cigarettes in stores. Right now we

have all these laws in all 50 states that prevent the sale of

cigarettes to minors, but none of them mention e-cigarettes

because they were all passed before e-cigarettes were invented.

We have laws that prohibit free sampling, but in my local mall,

which is the first one in the United States to go smoke free,

there's a kiosk now where you can get free samples of

e-cigarettes and you can step up and sample the wares.

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So we have these laws that have been very helpful in
reducing the number of kids who smoke, but e-cigarettes, it
doesn't apply to them. My first concern was when I saw a
television advertisement for e-cigarettes with a celebrity
endorsement. That's something that's been agreed to by the
tobacco companies to be unethical back since I was a kid, you
know. Since Ronald Reagan was hawking Chesterfields, we
haven't seen cigarette ads on TV, and yet now on the Internet
you can see celebrities hawking, you know, electronic
cigarettes. So the marketing strategies that worked to make
cigarettes so popular among teenagers in previous generations,
those restrictions don't apply to e-cigarettes, and so we're
seeing all the abuses that led to this epidemic of teenage
smoking, which led to the epidemic of adult smoking.
E-cigarettes are coming in under the radar, and they're using
-- some of the companies are using all the same marketing
tactics that worked so well in addicting previous generations,
so we don't want to see that.

And then finally there's no warning labels on
e-cigarettes. There's no warning there that they're addictive.
And the advertisements have no warnings. So these are
concerns. My concern is that the FDA needs to regulate these

products, if nothing else, just to apply the same marketing

standards to these new products that we've come to accept for

existing cigarette products for past generations. And I'll

stop there.

(Applause.)

DR. DRESLER: Thank you.

I know you're probably thinking that it's time for

clarifying questions, but no, yet another change to the

schedule. Because we are running ahead, we thought we would

have the next speaker, Dr. Steve Hecht, come present before

lunch, and then we'll do clarifying questions after him for

this last group of speakers and then we'll do lunch, okay?

So Dr. Steve Hecht from the University of Minnesota

speaking on Toxicant and Carcinogen Metabolites in the Urine of

e-Cigarette Users.

DR. HECHT: So I'm going to talk about the analysis of

urine of e-cigarette users for certain metabolites of toxicants

and carcinogens. I have no disclosures.

So several studies, some of which have been mentioned this

morning, have found carcinogenic and toxic compounds in

e-cigarette liquids and aerosols. These include tobacco-

specific nitrosamines, various aldehydes, polycyclic

hydrocarbons, and metals. But, in general, as you've seen, the

amounts are considerably less than in the smoke of tobacco

cigarettes, and there are still no standard methods for

measurement of e-cigarette constituents. There's a great

variety of products, and they're used under a great variety of

conditions, so we don't have a standardized way of comparing

these different products.

So our approach is to quantify toxicant and carcinogen

metabolites that we call biomarkers in the urine of e-cigarette

users, and that could be a more relevant approach to assess the

potential adverse effects. There have been limited studies so

far reported on this approach. We published a paper last

September that includes some of the data that I'm going to talk

about today, but not all of it. And then at the recent SRNT

meeting in Philadelphia, there were two papers presented

looking at biomarkers, and their conclusions were actually

quite similar to ours. So we compared biomarker levels in the

urine of e-cigarette users and cigarette smokers, exposure

biomarkers, which are related to exposure to specific toxicants

or carcinogens, and also biomarkers of oxidative damage and

inflammation. And the exposure biomarkers were discussed in

our recent paper, but not the biomarkers of oxidative damage

and inflammation; that's new data.

So the e-cigarette users in our study were 18 years or older, they were in good physical and mental health, stable on psychiatric medicines if they were using them. Importantly, they had not smoked cigarettes for at least 2 months, and that was validated to some extent by a measurement of carbon monoxide when they came into the clinic. And they were not knowingly exposed to secondhand cigarette smoke. They had to be using e-cigarettes for at least 1 month and 4 days per week. And the exclusion criteria were current use of nicotine replacement therapy or any other tobacco products or they were pregnant. They attended a clinic visit, completed a questionnaire, and we collected a spot urine sample. So we had 28 eligible e-cigarette users in the study.

And these are the brands that they used; they were mostly tank systems.

The average age was 34 years, 43% female, 93% white, 89% had some college education; they smoked an average of 21 cigarettes per day before switching to e-cigarettes.

Then we compared our e-cigarette data to data that we have obtained previously from analysis of urine of smokers. And for the exposure biomarkers, we used baseline data from four of our

previous studies. One was of 165 smokers of light cigarettes,

another was 40 smokers who were providing spot urine samples,

17 smokers who gave 24-hour urine samples prior to quitting,

and 18 smokers who were entering a nicotine reduction trial.

And for the biomarkers of oxidative damage and inflammation,

the comparison group were 86 smokers at baseline entering a

chemoprevention trial. And the demographics for the smokers

were similar to the e-cigarette users, and the methods were

essentially identical in both -- they're all based on mass

spectrometry.

So the biomarkers analyzed included 1-hydroxypyrene, which

is a biomarker of polycyclic aromatic hydrocarbon exposure;

total NNAL, which is a biomarker of NNK exposure; total NNN,

which is a biomarker of NNN exposure; 3-HPMA,

hydroxypropylmercapturic acid, which is a biomarker of

acrolein; HMPMA, which is a biomarker of crotonaldehyde; 2-HPMA

is a biomarker of propylene oxide; and SPMA, which is a

biomarker of benzene; and then, of course, cotinine, biomarker

of nicotine.

So just to review some of the characteristics of these

compounds. The PAH are ubiquitous products; they're combustion

products. Some of them are strong carcinogens. Benzo[a]pyrene

or BaP is probably the best known of these. It's rated as Group 1 by the International Agency for Research on Cancer. And NNK and NNN are powerful tobacco-specific carcinogens also rated as Group 1. Acrolein is a very strong irritant, a toxicant, as is crotonaldehyde. Propylene glycol is a carcinogen that -- propylene oxide, I'm sorry, is a carcinogen that could be formed from propylene glycol at high temperature. Benzene is a cause of leukemia in humans. And nicotine, of course.

So all of these compounds appear on FDA's list of harmful and potentially harmful constituents of tobacco smoke. Benzo[a]pyrene, NNK, NNN, acrolein, and benzene have also been recommended by WHO for mandated lowering in tobacco smoke, and crotonaldehyde is considered a high-priority compound for monitoring. PAH, NNK, NNN, and volatiles such as acrolein and benzene are considered to play an important role in cancer reduction by tobacco smoke.

So these were the results for the exposure biomarkers. So for 1-hydroxypyrene, the amount was 0.38 pmol/ml urine, which was significantly less than in cigarette smokers; total NNAL was 0.02, which was significantly less than in cigarette smokers, as was total NNN; 3-HPMA from acrolein, significantly

less than in cigarette smokers; HMPMA from crotonaldehyde,

significantly less; 2-HPMA from propylene oxide was

significantly less; and SPMA from benzene was also

significantly less. Only cotinine among these was

insignificantly different from the amounts in smokers.

And if we compare these levels to the levels in

nonsmokers, again, from the literature, the 1-hydroxypyrene

levels were almost the same as the levels found in the NHANES

study; total NNAL and NNN are not detected in nonsmokers unless

they're exposed to secondhand smoke; 3-HPMA from acrolein was

quite similar to the reported amounts for nonsmokers in the

literature because it's an endogenous compound. We all make

acrolein from lipid peroxidation, and we all make

crotonaldehyde. So, again, the levels in e-cigarette users

were similar to nonsmoker levels. Same for HPMA; it was

actually less. And SPMA.

Looking a little more carefully at the total NNAL data,

there were actually 4 of the 28 e-cigarette smokers,

e-cigarette users, who had higher than expected levels of total

NNAL. These ranged from about 0.26 to 0.95 pmol/ml. This is

way too high for secondhand smoke exposure. It's possible that

it might result from NNK in the e-liquids, although levels of

that are usually quite low, or perhaps there were a few

cheaters. Total NNAL was below the detection limit of 0.015

pmol/ml in 16 of the 28 e-cigarette users. And the remaining 8

e-cigarette users had an average amount of total NNAL similar

to secondhand smoke exposure, although we asked them all about

secondhand smoke exposure and they all claimed not to have been

exposed. So these are some questions.

As for oxidative damage and inflammation, the biomarker of

oxidative damage that we quantified was 8-iso-PGF-2α. It's an

oxidation product of arachidonic acid, and it's widely used in

the literature as a biomarker of oxidative damage, and it's

always elevated in smokers compared to nonsmokers. This is

based on some very large studies. Looking at median values

expressed as picomoles per ml, we didn't see any difference

between e-cigarette users and smokers. PGEM is a biomarker of

inflammation. It's a metabolite of prostaglandin E2. Again, we

didn't see any difference between e-cigarette users and

smokers.

When the results were expressed in picomoles per mg of

creatinine for the 8-iso-PGF-2α, we actually did see a

difference. The median value was lower in e-cigarette users

and smokers, and the difference was significant. PGEM, we saw

no difference. And when results were expressed as the mean

plus or minus of standard deviation and in picomoles per ml,

again, we didn't see any difference in e-cigarette users and

smokers.

Now, these e-cigarette users, remember, were supposed to

not have smoked for 2 months, and in the literature, the

decline of 8-*iso*-PGF-2α when a person stops smoking was

reported to be about 40% in 2 weeks, so if these individuals in

our study actually had stopped smoking and were like the ones

that are reported, then their values actually should have been

lower. But we don't know whether this is a hangover from

smoking or whether there's actually something going on with

e-cigarette use. So this requires further study. And the same

with PGEM. We didn't really see any difference between

e-cigarette users and smokers in this biomarker of

inflammation. But also in the literature, there's not that

great a difference between smokers and nonsmokers in PGEM. So

it's not quite clear what's going on here, and I think we need

more work.

So, in summary, levels of all the exposure biomarkers

decreased significantly lower in e-cigarette users than in

smokers, except cotinine. But the levels of biomarkers of

oxidative damage and inflammation were similar in smokers and e-cigarette users. So this requires further study because inflammation and oxidative damage are associated with tumor promotion, co-carcinogenesis, and other effects. That's our finding. Thank you very much.

(Applause.)

DR. DRESLER: And then, Steve, could I ask you to sit up towards the front because we'll do clarifying questions and have you more in a group.

Dr. DiFranza, if the bad taste of cigarettes increases the initial rejection, what would motivate adolescents to switch from a flavored e-cigarette that they like to a combustible cigarette that tastes bad?

DR. DiFRANZA: I guess if the e-cigarette wasn't giving them as much nicotine as they needed to satisfy their addiction, that might cause them to go to a product that would deliver more nicotine. But I'm sure it wouldn't be for the taste though.

DR. DRESLER: I just have to add, you had that part about chocolate up there, and many people know that I'm serious about chocolate -- so anyway.

This one is for you also. What evidence is there that the

phenomenon you describe occurs with e-cigarette use? You rely

entirely on data about smoking, which is much more complex and

otherwise a different exposure.

DR. DiFRANZA: Well, this -- I did only cite cigarette

smoking, but we've also looked at chewing tobacco users,

smokeless tobacco uses, and we gave them three different

measures of nicotine addiction, and so the idea is that

cigarettes deliver nicotine in a rapid bolus that reaches very

high levels, and the nicotine from the chewing tobacco comes up

very slowly over hours, so they're almost opposites. And youth

and young adults use the smoking tobacco, use the smokeless

tobacco, had exactly the same symptoms of addiction as those

who had smoked cigarettes and in the same proportion. So there

are many different symptoms that we're looking at, and the

profile of which symptoms are most common and which symptoms

were least common were exactly the same in both chewing tobacco

users and the cigarette smokers, so I expect that the

e-cigarettes wouldn't be any different. And nicotine is

nicotine.

DR. DRESLER: Thank you.

Dr. Hecht, in the urine analysis, how long does it take

for inflammation for a smoker who quits to go to nonsmoker

levels?

DR. HECHT: I couldn't find good data on PGEM when people

stop. I couldn't find it in the literature. But for the

oxidative damage, as I mentioned, the 8-*iso*-PGF-2α decreases in

about 2 weeks, and then if they start smoking, it goes right up

again.

DR. DRESLER: Thank you.

All right, okay.

Dr. Hecht, have you analyzed biomarkers of exposure to

formaldehyde among e-cigarette users?

DR. HECHT: So we've got a proposal to do that, to look at

formaldehyde DNA adducts. We haven't done it yet.

DR. DRESLER: Thank you.

Are there any other cards floating around? Yes, okay.

Thank you, sir. All right. You guys just want to go to lunch,

I think is what it is.

Dr. Suter, have you studied transplacental effects of

heavy metals like cadmium? So transplacental effects of heavy

metals.

DR. SUTER: Sure. Cadmium has been extensively studied in

the literature. It does accumulate in the placenta and does

cause changes to placental function. One of the biggest

researchers in this field is Richard Miller at the University

of Rochester. I have myself not done this.

DR. DRESLER: Thank you.

So that's the clarifying questions for now. Again, we'll

have a session this afternoon for a panel we can address

questions to.

It's lunch time. I have 11:40, let's call it. So we'll

be back at 12:40. Okay, so back at 12:40, please. Thank you.

Cafeteria to your left or for the buffet, and then the

cafe to the right.

(Whereupon, at 11:38 a.m., a lunch recess was taken.)

A F T E R N O O N   S E S S I O N

(12:43 p.m.)

DR. DRESLER: Our plan was -- as you know, we've been a little bit ahead of schedule today, and the next person on the schedule is Chris Bullen, who is going to call in from New Zealand, who -- I think it's 5:45 a.m. there. So we're working on reaching him. We have his slides, but that's a work in progress right now.

So we're going to move to the next speaker, who is Dr. Michele, Theresa Michele, from the FDA Center for Drug Evaluation and Research, and she is going to speak on considerations regarding approval of drugs delivered by inhalation.

Dr. Michele.

DR. MICHELE: So good afternoon. My name is Terri Michele, and I'm the Director of the Division of Nonprescription Drug Products in the Center for Drug Evaluation and Research. We're responsible for the review and the regulation of over-the-counter drug products, including many of the nicotine replacement products indicated for smoking cessation and the division under which e-cigarettes would fall if being evaluated for an OTC drug claim. I'm also a

practicing pulmonologist, so I was especially appreciative of

the folks from CTP asking me to speak regarding pulmonary

safety testing for inhalational drug products such as

e-cigarettes.

By way of disclaimer, I have no conflict of interest, and

these slides, like all slides that you see from the government,

are not intended to convey an official position of FDA.

So what you'll hear from me today are the practical

considerations for inhalational products such as e-cigarettes

from a clinical standpoint for drug development. This is not

intended to be an exhaustive list of everything that FDA would

want. This is just a starting point, and it's painted with

very broad brushstrokes. So I'm going to start off with a

general approach that we use at CDER to talk about the

development of pulmonary safety for inhalational products.

There are a lot of other systemic considerations that I will

not be discussing today. I'll then talk about some more

specific points related to e-cigarettes, and finally, I'll

conclude with some comments on over-the-counter considerations.

Just to put everyone on the same page, I'll start with the

somewhat obvious statement that inhaled products can deposit

anywhere along the respiratory tract. As such, when we look at

inhalational products, we have to consider tissue exposure of the entire respiratory tract, from the oral cavity all the way into the deep lung. As you heard in the opening session yesterday, there are all sorts of factors that affect the pulmonary delivery of drugs. These include the emitted dose from the device, the airflow rate from the patient, the particle size distribution of the drug, and the deposition of the drug along the respiratory tract.

So as a starting point for drug development, it's important to consider the safety of the drug product as delivered to the patient. So what do I mean by that? Essentially, it's not just the active ingredient, in this case nicotine, that we care about, but it's actually everything related to the drug, including the excipients, the contaminants, the heated aerosols, whatever goes into the patient. All of these things are, of course, affected by the device and by how the patient uses the device. One common misperception that we hear from drug sponsors is that the only relevant drug characteristics are for the drug substance, and that is what goes into the device. While that's certainly important, we also care about what comes out of the device because this is what goes into the patient.

This is particularly important for e-cigarettes where the drug substance is vaporized, which changes the chemical constituents of the drug. Before going into human clinical trial, it's necessary to characterize what we're giving people from a chemistry standpoint and also to assure some level of safety in animals.

Finally, we've learned, with inhalational products, that seemingly very small changes in the device can lead to very big changes in the drug delivery to the patient. As such, we request that sponsors test the to-be-marketed device. This is likely especially important for e-cigarettes because you've already heard a lot about how variations in the device vary the nicotine and other particle delivery to patients. So let me emphasize this again. Make sure you run your clinical trials with whatever drug, device, product you intend to market.

While I don't intend to talk about toxicology studies in detail, I just want to mention a couple of points that are driven by the clinical use of the drug. So, first, if you have an inhalational product, you have to look at inhalational toxicity. As I mentioned previously, this doesn't apply just to the active ingredient, but to all of the other components that are inhaled by the patient as well.

Another consideration is the use of the product and what constitutes chronic use. So FDA considers that a product is used chronically if it may be used for 6 months or more over the course of a patient's lifetime. Using this definition, most over-the-counter drugs are considered chronic use drugs, even though many are labeled for use only for 10 to 14 days at a given time. Nicotine replacement products are no exception because a patient may attempt a quit attempt more than once in their lifetime. Drugs that are considered to be for chronic use generally require chronic toxicology and carcinogenicity data as part of their development.

To support the pulmonary safety of an inhalational product, we generally require both short-term and long-term pulmonary safety trials. This applies both to products that are intended to have a primary effect in the lungs, such as bronchodilators, as well as products intended to have systemic effects, such as nicotine, for which the respiratory tract is just serving as the route of delivery into the bloodstream. For short-term pulmonary safety, we're primarily concerned with acute bronchospasm, which is evaluated using pulmonary function testing with a primary endpoint of the forced expiratory volume in 1 second or FEV_1.

We also look at adverse events with a particular focus on respiratory adverse events and also on the need for rescue medication. These are really pretty straightforward studies with short-term endpoints and a relatively small population. Finally, we recommend that these studies be done in three different patient populations based on the airway hypersensitivity of the population. First, we look at healthy controls. This is really just to make sure that we aren't seeing anything too egregious in terms of bronchospasm before we move into the other populations. We also test the asthma population. This is essentially the worst-case scenario because this is the population most likely to respond to a bronchoprovocation challenge. And then for products that are used in populations where there is increased incidence of smokers, we recommend testing the COPD population because this is the area of lung disease that's most likely to occur in the population that's using the product.

This is a graph of what's looked at with spirometry testing. After maximal inhalation, the forced expiratory volume in 1 second, or FEV_1, is measured usually in liters, and this is the volume that a person can forcibly exhale in 1 second after taking their deepest breath. The subject is told

to blow out as long and as hard as they can, and looking at the curve which plots volume in liters over time in seconds, you can see that a normal FEV_1 is usually more than 80% of the person's forced vital capacity.

So in this slide I provide an example of a short-term pulmonary safety trial in asthmatics. This graph comes from the approved product label of Adasuve, which is an inhaled version of the antipsychotic loxapine. Even the loxapine, when given by injection, has a very long history of safety. When inhaled, it causes significant bronchospasm. Based on short-term pulmonary safety testing, this product was approved with a very restrictive risk evaluation mitigation strategy, or REMS, permitting its use only in facilities with immediate access to advanced airway management personnel and equipment. In this graph, loxapine is shown in blue and placebo is green. The red arrows denote dosing. After the first dose, you see an abrupt drop in FEV_1. You then see a return to baseline in about 2 hours followed by a gradual decline beginning at 4 to 6 hours; it's consistent with the late asthmatic response. Following a second dose, you get a more profound nadir which does not return to baseline.

In addition to short-term pulmonary safety, we also

request long-term pulmonary safety trials, in this case looking

at a patient population that is representative of who would use

the product. The goal of the long-term pulmonary safety trial

is to assure that there's no chronic decrease in lung function

over time, such as that described yesterday with the popcorn

factory workers with bronchiolitis obliterans. Primary

endpoints are generally FEV_1, and adverse events, again, with a

special attention to respiratory events. The duration of the

study is expected to take into account the expected duration of

use of the product, again, factoring in the fact that the

product may be used multiple times over a lifetime.

Here I provide an example of a product that was found to

have long-term effects on lung function. This comes from the

package insert, the approved product label for Afrezza, which

is a recombinant human insulin. Looking at FEV_1 over time,

Afrezza is in the lower graph with the filled-in circles, and

the comparator, which was other diabetes treatments, were in

the open circles. In this case, the separation occurred

primarily in the first 3 to 6 months and became stable after

that. This product was also approved with a REMS.

One other area that's often overlooked but that FDA

expects in the development of any inhalational drug device

combination product is collection of information on device

performance in clinical trials. Again, I'm not here to talk

about devices -- that was covered very nicely in the December

workshop -- but just want to highlight the need to collect

data. Before taking a device into clinical trials, we expect

testing of ruggedness and reliability. Remember that

everything in clinical trials and in patient hands follows

Murphy's Law: If it can go wrong, it will go wrong. And

that's what we're here to test. During the clinical trial,

it's important to test all devices that the patient in the

study reports as malfunctioning and also to look at a sampling

of devices that were not reported. Finally, we request human

factor studies to evaluate the usability and the instructions

for use.

   Now that you have the overview of what we expect, I'll

just make a couple of comments about e-cigarettes. First, I

want to note that e-cigarettes developed for a therapeutic

purpose are considered to be drug-device combination products

with a drug primary mode of action. This means that CDER is

the lead center with CDRH consulting, and if you're developing

the product for OTC use, it would come to the Division of

Nonprescription Drug Products. Second, just as laid out for

other inhalational drug products, the safety of your

e-cigarette product must be fully assessed and not just

compared to combustible cigarettes. When assessing safety,

remember that inhalational toxicity is a concern regardless of

the intended site of nicotine delivery. That means that even

if you are developing a product for which you intend delivery

into the oral cavity, we still care about possible pulmonary

toxicity. I'll also remind you that all excipients must be

qualified for inhalational use. That means that flavor

additives that are considered to be generally recognized as

safe are not considered to be generally recognized for safety

in the lung unless you show it. Finally, although not strictly

a safety issue, I remind you to assess the potential for abuse

and misuse as part of your development program, including

accidental exposure in children.

Dr. Stansbury is going to be covering OTC drug products

and some of the clinical trials that we expect as part of our

consumer studies later this afternoon. I'll just mention that

there are a number of them that we generally require, including

label comprehension studies, self-selection studies, actual use

studies, and the human factor studies that I already mentioned.

Finally, I just want to close by encouraging you to talk

to the Division at appropriate times in your development

program. Development of a drug-device combination inhalational

product is very complex, and sponsors generally benefit from

interaction with the Division.

I provide contact information here, and our project

manager, Commander Alina Salvatore, is available to receive

your calls.

Thank you.

(Applause.)

DR. DRESLER: So our next speaker would be Chris Bullen.

Has he called in? Dr. Bullen is in New Zealand, and we had

hoped to have him call in as we showed his slides.

No, okay. All right. So we'll leave that line, and if we

can -- we'll try and get a hold of him to see if we can't catch

up with him later, but that means the next thing -- actually,

the next thing that I would like to do is any questions for

Dr. Michele. So we cut her session shorter and split it by

lunch and made it even shorter, so let's see if there's any

questions first for Dr. Michele.

You get to use cards, Peter.

(Laughter.)

(Off microphone comments.)

DR. DRESLER: Do we have any -- no others. I see a couple scribbles going quickly, so it means you are going to get a question coming forward.

But to be clear, so -- because I'll ask one. You showed, for the human insulin, inhaled human insulin, that you did have a decrease in FEV_1 that was consistent, persistent across use of it, and it was still approved.

DR. MICHELE: That is correct. So just to comment on that, when we look at approval decisions, we always weigh the benefits of the product versus the risks, and we do whatever we can to minimize those risks. In this case, both of the products that I showed had some pulmonary toxicity that were shown in these studies, but were determined that the benefits would outweigh the risks for certain populations, and as such, they were approved with fairly restrictive risk evaluation mitigation plans to try to minimize the risk.

In both cases, these products contain in their labels statements that say you shouldn't use them in asthmatics, you shouldn't use them in COPD patients, so those are the patient populations that were demonstrated in studies to have the greatest risk. There are further things in the REMS plan, for example, for Adasuve. You can only get it in facilities where

you've got intubation equipment readily available, but given

the fact that it's being used as an acute antipsychotic largely

in emergency room situations, in that case, it was felt that

not having to get close to a person with a needle was going to

calm them down sooner and give them the opportunity to perhaps

not be hospitalized. So that was the risk-benefit equation

that the FDA weighed.

DR. DRESLER: Are you familiar with the UK MHRA's approach

to regulating nicotine-containing products?

DR. MICHELE: I'm not. I'm actually not familiar with

that, and hopefully we'll have the opportunity to hear from

some of you who are familiar at some point.

DR. DRESLER: Okay. So he's right. It's longer, but

that's good. Thank you. But I can read it, Peter.

E-cigs are a different beast. Name.

(Off microphone comment.)

DR. DRESLER: There is a strong rationale and precedent

for testing and approval, as you described, but for

e-cigarettes, they're already on the market. Wouldn't this be

more like a food? We don't need approval to --

UNIDENTIFIED SPEAKER: Test raspberries.

DR. DRESLER: To test raspberries?

UNIDENTIFIED SPEAKER: Yeah, in cancer --

DR. DRESLER: It is. It is what it says. I just -- I'm sorry. I had that disconnect, sorry. So to test raspberries in cancer prevention. Are there mechanisms to deviate this for a typical IND process? So basically you're saying that, you know, why isn't this more like a food versus a drug, and is there mechanisms to deviate, then, for something that's already on the market, already being used from typical --

DR. MICHELE: Right. So there's one key point here that I think folks may be missing, and it was very carefully stated in the slides and also in my voiceover, is the point of therapeutic purpose. So the key point is that if you are testing these products for a therapeutic purpose, i.e., for smoking cessation or to cure cancer or to, you know, treat your arthritis, then that's a therapeutic purpose, and that falls under the drug laws.

DR. DRESLER: Any others? Yeah, okay. And you, of course, are getting them all since you were the only one in this session, you lucky person.

Okay. Are there any approved flavored inhalants, and if so, could you please provide examples? So any -- we heard a lot yesterday about flavors and perhaps any concern about those

toxicities, so are there any approved flavored inhalants?

DR. MICHELE: So there are no drug products that are inhalational drug products with flavors.

DR. DRESLER: Do you know, this is another question that came up too. Can I follow up?

How about colorings? So not flavorings, but colorings. Are there any approved colorings for inhalation?

DR. MICHELE: Not that I'm aware of.

DR. DRESLER: Okay, all right.

So are you considering e-liquid with nicotine to be an over-the-counter product? And I think you addressed this with your therapeutic claims, but I may let you do that.

DR. MICHELE: Right. So in terms of over-the-counter versus prescription, that is the sponsor's choice. If a sponsor chose to come in with an e-cigarette for prescription use only, that would be perfectly okay. The reason that I'm talking about it in terms of over-the-counter use is that we do have many nicotine replacement products that are over-the-counter, and so most of the interests that we've heard at FDA in terms of looking at these as drug products has been for over-the-counter use. But that's really the sponsor's choice, and if you wish to pursue a drug claim for an e-cigarette

product, that would most likely go to the Division of

Anesthesia, Analgesia, and Addiction Products or DAAAP, as the

primary division.

DR. DRESLER: Within CDER?

DR. MICHELE: Within CDER, yes.

DR. DRESLER: All right.

What is the average cost of a product to comply with the

studies that you had listed? Do you have an idea of what those

-- that development cost would be?

DR. MICHELE: Right. So I'm actually not the best person

to ask that. I know we have a number of pharmaceutical

representatives in the room, and they could probably tell you

off the top of their heads. I will say that the short-term

pulmonary safety studies are not big, huge studies. These are

short-term studies that can be done with a cohort over the

course of a couple of days, you know, you're only talking about

1 to 2 days of actual study time, and you're not talking about

huge numbers in each treatment group. The long-term safety

studies are by definition long term, and those are more

difficult. However, you can do those -- be creative. You can

do those as part of your development program, so you may tack

those on with an efficacy and safety study. They don't have to

be standalone trials.

DR. DRESLER: Okay, thank you very much. And thank you
for standing up there and being the sole person to take all
that. Thank you.

Okay, so we're now going to go to the panel. So the panel
speakers, do you all know who you are? Where did I put my
list?

Dr. Bailey, Dr. Benowitz, Dr. Hecht, Dr. Oncken.

(Pause.)

DR. DRESLER: Questions on cards working their way in.
This is your chance to ask the questions from all day.

So could you please introduce yourselves? We're starting
at that end, Dr. Hecht. Introduce yourself, say your
institution and any declaration of interest and then -- yeah,
let's do that because I was asked, and we did it yesterday even
though you guys all put up your disclosures in slides earlier
except for you, Dr. Benowitz. So let's just do it again, okay?

DR. HECHT: Steve Hecht from the Masonic Cancer Center,
University of Minnesota. And I have no conflicts to disclose.

DR. ONCKEN: Cheryl Oncken from the University of
Connecticut Health Center. I have done smoking cessation
trials with pharmaceutical company studies.

DR. BENOWITZ: Neal Benowitz, University of California, San Francisco. I'm also representing the American Heart Association. I have consulted with pharmaceutical companies, and I have been a paid expert in lawsuits against the tobacco industry.

I would also like to say, on behalf of the Heart Association, that they have prepared a guidance to employers on integrating e-cigarettes and ENDS into tobacco worksite policy, which was published in the *Journal of Occupational and Environmental Medicine* this week, if someone's interested in reading that. I think it's the first guidance for the workplace.

DR. BAILEY: I'm Bill Bailey from Birmingham, Alabama, the University of Alabama in Birmingham. I'm a pulmonologist. I have not really had any conflicts of interest in the last 3 years, but in the past I have done pharmaceutical studies with almost all the different companies, but more in pulmonary disease studying drugs that might improve asthma and COPD rather than smoking cessation products. I've also served as an expert witness in a case to provide the risks and benefits of Chantix in a case where Pfizer was involved. And I think that's about it.

DR. DRESLER: Okay, all right.

All right, so the first question we have is, we had talked about it earlier, the health effects in individuals with underlying heart -- and in pregnancy, but what about patients with other chronic disease? So cancer, diabetes, mental health disorder.

And, Steve, I think you did touch on that with some of the carcinogens, but can you talk about what some of the health effects are from e-cigarettes from what you know, what we've heard about, in cancer, diabetes, or mental health?

DR. BENOWITZ: I'll start there. There has been very little research. I think they're important questions. I'd say, first of all, at least from a cardiovascular point of view, if e-cigarettes were helpful in people quitting, I would want my cardiovascular patients to have access to them because they're at such immediate risk. I think that would be a good population actually to do safety studies in. I'd also like to say that there is one study that I am aware of done by Riccardo Polosa; it was not a well-controlled study. It was done in Italy. But they looked at asthmatics who were smokers, and they looked at pulmonary function tests over time, and those asthmatics who used e-cigarettes to quit smoking had improved

pulmonary function compared to those who continued to smoke,

which also brings up a regulatory question that I'd like to ask

Dr. Michele.

If you had a product that was -- that had some toxicity,

say it had an inflammatory response in a healthy person, but

you found that in someone with disease and they used it and

smoked less or quit smoking, their pulmonary function got

better, how would the FDA evaluate that, which could be a

health benefit even though there might be some short-term

toxicity, to help the person?

DR. MICHELE: So I don't know that that's really an

answerable question in the abstract. I'll just comment that

for each product we look at the benefits and we look at the

risks. And the important point is that you have to assess all

of those risks as well as all of those benefits so that you

know what you're comparing.

DR. BAILEY: May I say something on the Italian study that

you -- Neal referred to? It's like all the studies that are

pro and con. It's kind of useless. It was a 12-man study with

no control, and so they used the baseline as the comparison,

and when you use the baseline and you put them in a clinical

trial and take care of them for a year, people do better in a

clinical trial just by taking their medicines better and other

things compared to what they were doing at baseline.

So I've done a number of studies where we were dealing

with behavioral issues such as asthma, you know, taking your

asthma medicines and dealing with those kind of things, and

those in their intervention group improved more, but the

control group improved significantly to the point of being

better than their baseline, so that just happens. But you can

answer the question with a large study with controls, but there

are no large studies with controls to deal with many of these

health effects, and that's just a dearth of information.

I would like to say that if you could really get people to

quit smoking, you know, we don't know exactly what the risks of

e-cigarettes are, but I can't imagine that they would be worse

than cigarettes. I think there might be some unexplored issues

with some of the abnormalities that might be discovered, but

that would be great. But the problem is I don't know that we

know yet whether we can get our patients to quit smoking with

e-cigarettes. The only -- but that's a very important question

to answer.

DR. BENOWITZ: Can I just make one quick response? I

agree with you totally about the small n and that it's not

definitive, but their control was people with asthma who did

not quit smoking, and the people who quit smoking with

e-cigarettes had better pulmonary function than the ones who

kept on smoking, so that was the way they tried to control --

oh, I agree it's not a great setting.

DR. BAILEY: Well, then --

(Off microphone comments.)

DR. DRESLER: Microphone, microphone.

DR. BAILEY: I'm sorry. I've got a thing in a packet of

material that did use the baseline for control, and it was an

Italian study, so it must have been a different -- and there

are a lot of little small studies out there.

DR. ONCKEN: And I just want to comment on the fact on

mental illness. One of my jobs is working in a general

medicine clinic, and we're increasingly seeing people with

schizophrenia, a number of different mental illnesses that are

using electronic cigarettes, and they've typically been

excluded from trials, and I really think that this is a

potential benefit in this population and they should

potentially be included. And I guess one other thing, looking

at in clinical trials, one of the things that you would want to

look at is if for some reason, for any reason that this is

potentially making an underlying condition worse or better.

DR. DRESLER: Okay.

Neal, I know that you've looked at the issue of diabetes. Would you want to go anything near what you think about e-cigarettes, diabetes versus -- and e-cigarettes versus conventional cigarettes?

DR. BENOWITZ: I think it's a great question. We know that nicotine induces insulin resistance and therefore can make diabetes worse, and that smoking is a risk factor for Type 2 diabetes. There's some evidence that NRT can also impair insulin sensitivity. I would assume e-cigarettes would do the same thing. But the more important thing about cigarette smoking is because of the oxidants and inflammatory response, it markedly interacts in terms of increasing cardiovascular risk. And I would hope that e-cigarettes at least would not do that part of it.

DR. DRESLER: And there's a question that came up yesterday, and maybe this panel could address it. There's a concern over dual use, and so if everyone switches over to e-cigarettes, you know, is that better across the board, whether in pregnancy or cardiovascular? So does this panel know anything about how many cigarettes per day actually

increase that health risk?

And, Neal, I know you were like reading something, so that's actually a question -- I think you've addressed that before. So is there -- let me repeat it in a simpler question.

How many cigarettes a day can you smoke before you start to get some of that health impact? So it goes after the issue of dual use, right? And so are you going to get the full, perhaps less harm, benefit from e-cigarettes in switching to that if you still have some dual use? And how much is dual use?

DR. BENOWITZ: I think there are two issues. One is if you had people smoke fewer cigarettes, if you tried to make someone smoke fewer cigarettes without giving them nicotine, actually take in much more smoke per cigarette, and so there's very little evidence of any benefit of trying to make people smoke fewer cigarettes. If you give them nicotine as well, then I think several studies have shown that you can substantially reduce toxicants. Then the question comes about the dose response of those toxicants for particular diseases. And I think for lung cancer, you know -- and Steve could talk more about it. I think there's generally a linear correlation between toxicant exposure and lung cancer risk.

For cardiovascular disease, as Aruni showed earlier, the dose-response curve is very nonlinear, so risk goes up with the first few cigarettes a day, so smoking 5 cigarettes per day or so is at least 50% of the risk of smoking 20. So I think the cardiovascular benefit would be relatively small, but there may be benefit for cancer or COPD, but I'd like to see what Steve thinks about that.

DR. HECHT: I think it's pretty obvious that e-cigarettes are going to be less carcinogenic than tobacco smoke. You only have to look at the composition of tobacco smoke with more than 7,000 compounds and more than 70 established carcinogens. E-cigarettes can't match that. E-cigarettes may have some problems, but I think with respect to carcinogenesis, there's no comparison.

DR. ONCKEN: And I just want to add, talking about different diseases, in pregnancy, even smoking one or two cigarettes a day actually increases health risks for some of the placental accidents would -- so I don't think dual use would potentially be beneficial.

DR. BENOWITZ: Just to follow up on that. You showed data, and I think you have your own data, showing that reducing by a few cigarettes per day with NRT can also have beneficial

effects on body weight, right? On the birth weight of the

baby.

DR. ONCKEN: This is true that we did find some effects,

but to eliminate all risk, that's what I was referring to.

DR. DRESLER: Okay.

Speakers this morning raised concerns about HPHCs in the

aerosol, and yet many of the data cited showed examples of not

detectable. Are there potential opportunities to learn from

this and even establish best practice for e-cigarette design?

(Off microphone comment.)

DR. DRESLER: You got to turn the microphone on.

DR. BAILEY: If it's a pulmonary question, I still don't

know the answer. But, you know, I think that we do need to

know a little bit more about the particles there. And yeah, I

think that the more you know and the more you find with things

that could be improved, the better you can do the design of the

e-cigarettes. But, quite honestly, the details of the question

you asked, I don't really know anything about it.

Does that help? Helps put me in my place.

DR. BENOWITZ: I'm not sure what the question was asking,

but I would just make the comment on Bill's study that he

showed this morning where he showed an inflammatory response in

the lung, which to me is really a very important endpoint,

because chronic inflammation is a major way that cigarette

smoking causes disease and may start in the lung, affects the

lung and affects the cardiovascular system as well. So if

you're able to identify constituents of the electronic

cigarette aerosol that produced inflammation and if you could

take that out, that would be a very important way to guide a

product, as for example, choline. If you found out that the

choline caused it and you took that out, I think that would be

very important. So I think there are some potential ways to

combine toxicology studies with looking at the constituents of

the aerosol.

DR. HECHT: Even though the levels of contaminants in the

nicotine have been shown so far to be low, I think that if

you're talking about best practices, you need to purify the

nicotine that's going to go into these things. So, I mean, I

think that there's probably nicotine from all kinds of

different sources being used and the nicotine needs to be

cleaned up.

DR. DRESLER: Okay.

All right, so we've talked about risks to certain groups

of people. What about studying the benefits of using

e-cigarettes? Wouldn't people with lung and heart disease feel

better if they used e-cigarettes? Shouldn't we be studying

that, how much better they feel?

DR. BENOWITZ: I think that is a great question. It's

difficult to do that, so what many of us in practice have done

is if someone comes in, if someone's a smoker, we try to get

them to quit smoking with the standard approaches. And if

someone says I've tried and that's failed, I'd like to try

e-cigarettes, I think it's quite reasonable to be supportive.

As we know, it's impossible to do a proper clinical trial,

which I would like to do if that was available, because I think

it would -- e-cigarettes might be a very useful tool for

cardiovascular patients. But at the moment, we can't do that.

DR. DRESLER: Why can't you do that?

DR. BENOWITZ: Because you can't do a therapeutic clinical

trial with the current guidelines from the FDA without having

an IND, which at least I can't get.

DR. ONCKEN: Because you'd have to know all the

information available for an IND on electronic cigarettes, and

that's not available to people who would want to potentially

research the benefits.

DR. DRESLER: Okay.

So here's the next question. Do you believe the negative media on e-cigarettes will have a negative effect on population health because all the people who are turning -- returning to cigarettes from e-cigarette use, it's out of fear instilled by the negative news stories? So, you know, with all the information that's coming out saying bad stuff about e-cigarettes, do you think that's having a negative effect on population health?

DR. BAILEY: I'll just give a brief comment on that, and I'd like to hear the others. I don't think so, because I think there's still plenty of negative media coverage about cigarettes. In other words, recently there was a big story that was in most of the newspapers about the latest Surgeon General's report about all sorts of new diseases, increased number of cancers, and other things that are not possibly related but are definitively related to cigarettes. And at this point, I think most of the negative stuff about e-cigarettes are that we don't know, there are possible things that might be wrong with them, but I think it's not -- there are no definitive stories that say this causes cancer, whereas there are definitive stories that cigarettes cause cancer. So I can't imagine it would.

DR. ONCKEN: I agree. I think that studies that have

surveyed individuals who are smokers feel like it's less

harmful and that it has a less negative impact.

DR. DRESLER: Okay, Dr. Hecht. You measure the toxicants

and carcinogen metabolites in urine. Some of the chemicals or

parent compounds are ubiquitous. How did you determine that

they came from exposure to the use of e-cigarettes in your

studies?

DR. HECHT: Well, we're just comparing to levels that we

see in smokers and nonsmokers from other studies, so in many

cases, for example, acrolein, which is an endogenous product,

we all have acrolein metabolites in our urine, so what we see

in e-cigarettes was similar to what we see in nonsmokers. So

we can't really say where it comes from, so we just compared in

the study what we see in e-cigarettes to what we see in

smokers.

And smokers obviously have the additional impact of the

mixture in the cigarette smoke, so that's why all the exposure

biomarkers are higher in smokers. But we all have levels of

polycyclic aromatic hydrocarbons and volatiles like acrolein

and benzene; we're all exposed to these things or we produce

them in normal metabolism, so I think the only way we can

really find out what's going on in e-cigarette users versus

smokers is to do a longitudinal study where we really follow

these groups and compare what happens.

DR. DRESLER: Well, that leads right in to the next

question, so given that many e-cigarette users are former

smokers, how can you separate the health effects from

e-cigarette use from the long-term effects of years of smoking?

What unique issues should be considered in the evaluation for

short- and long-term health effects from dual or poly-tobacco

use, and how do you evaluate that?

DR. HECHT: I don't think you'll be able to -- it will be

very difficult to disentangle the effects of e-cigarette use,

if any, from the effects of smoking in individuals who have

done both, who are ex-smokers and then went to -- I think that

will be extremely difficult. What you're going to need do is

have groups of people who just use e-cigarettes and didn't

smoke and compare that to non-users.

It's almost like the smokeless tobacco studies. They're

very hard to do because a lot of smokeless tobacco users were

or are also smokers, so it's almost impossible to disentangle

because smoking has such a massive effect, and if you have

something that hasn't maybe -- not harmless, but has a

presumably lower effect, it's going to be hard to disentangle

it from smoking unless the person has never smoked.

DR. BENOWITZ: Yeah, I think we do have some disease

states that have shorter times of presentation compared to

cancer. So we know, following on myocardial infarction, that

if someone quits smoking and you look at 10-year survival, it's

twice as good compared to someone who continued smoking. It's

even better than someone who was a nonsmoker because there's a

major reversal of risk factor. So it would certainly be

possible, just like Bill talked about, with looking at lung

disease changes over time, you basically look at people who

used e-cigarettes to quit smoking compared to those people who

kept on smoking and those who quit smoking without using

e-cigarettes, and I think you can get a general idea of what's

going on.

So I think there are ways to approach that, not for all

diseases. To follow up on what Steve said, for smokeless

tobacco the best epidemiology comes from Sweden where it's been

a cultural thing for 40 or 50 years, and that's how long it

took before you got epidemiology studies. And so I think it's

hopeless for us to do that for e-cigarettes.

DR. ONCKEN: And I was going to say the same thing. You

really just have to have a longitudinal study following these

groups, somebody that smoked and went into e-cigs, a group that

continued to smoke, and a group that quit. But the problem is

that they're not going to be random, so there may be

differences in people that actually chose to use e-cigs to quit

versus those that continued to smoke, which could have an

impact on your health outcome, so that would be the problem.

But I think that's really the only way you could get some data

on that.

DR. DRESLER: Bill, did you --

DR. BAILEY: Yeah, I was going to say this is not perfect,

but we plan to try to recruit -- you can't really either give

e-cigarettes or cigarettes ethically to people who are not

smoking them, so that would be the purest way to randomly

distribute to see what happened over time or with specific

short-term tests such as methacholine challenge, but you can

find cigarette smokers who have never smoked e-cigarettes and

e-cigarette smokers who have never smoked cigarettes.

Both of those populations -- you know. And so that's one

way to do some short-term work. And one of the things that I

think would be interesting is bronchodilator response and

methacholine challenge in those two groups. Now, they're not

pure because the cigarette smokers are probably older and the

e-cigarette smokers, there's never -- they're probably younger,

and there are probably many other variations in their

demographics that you'd have to try to adjust for. And so even

though it's not perfect, I think you could learn something from

that.

DR. DRESLER: Okay.

All right, here is a question that's been around for quite

a while in the tobacco control environment, the lethal dose of

nicotine. This goes: What is the lethal dose of nicotine?

2014, lethal dose of 1 mg/kg was disputed by Mayer et al. In

fact, recent poison cases where ingestion of nicotine exceeded

200 mg did not result in a death. This is probably due to the

powerful medic effect of nicotine. Do you agree that the

lethal dose level of nicotine should be reevaluated?

DR. BENOWITZ: Yes, but it depends on what else is going

on, what kind of support you have. If you have someone in a

hospital, you could basically -- you know, if you treat them,

you can ventilate someone because most people who die, die

because they stop breathing. You look at someone untreated,

and it's hard to know. I think the study that came up with the

6 mg/kg was fairly convincing to me, so I think that the lethal

level in general is probably more than 0.5 mg/kg. As you said,

a lot of poison centers have seen exposures that are much

greater. Once you get someone in care, though, they should not

die. So the question is, you know, where are they at the time.

DR. DRESLER: Okay. Anyone else want to -- all right.

So I have heard that Chris Bullen is on the phone, so if

you guys want to stay there, please, if we will then -- you can

see the screen in front of you. We're going to -- I feel like

a television monitor on CNN or something because we're going to

go to New Zealand now.

(Laughter.)

DR. DRESLER: Then we'll come back and finish up with a

few more questions, okay?

Dr. Bullen, are you there? Washington, D.C., calling

Auckland, New Zealand. Dr. Bullen?

(No response.)

DR. DRESLER: Okay, I'm going to go back and ask some more

questions, then, until you let me know, okay? All right.

So another question we have is what specific organ system

-- so we talked about the lungs, we talked about the heart, and

pregnancy. What other organ systems do you think, besides

those three that are pretty important, what other ones should

we be focused on?

DR. BENOWITZ: So I think one really critical one is actually part of the lung, but in a way it's not. Infectious diseases, which are not often thought about, are actually a major cause of morbidity and mortality from cigarette smoking. And that's actually a model where I think one could do some reasonable sub-acute exposure studies, look at effects on experimental infections in animals and things like that, so I think respiratory infection as a target is a really important one.

DR. DRESLER: Makes me think of the conversation we had this morning, the presentation on the oral microbiome and how that might impact the disease in people who are using e-cigarettes or cigarettes.

DR. BENOWITZ: And just to follow up on that, one question I had that I didn't get a chance to ask is the relationship between oral microbiome from an oral product and the gastrointestinal microbiome where there is some concern about health effects, and so where you go to establish the health effects of changes in the microbiome. I think that's a really important question.

DR. DRESLER: Dr. Bailey, did you --

DR. BAILEY: Well, I would completely agree about the infections. Refractory infections are a big cause of morbidity and mortality. And cigarette smokers, we know, are at greater risk of various infections, and we don't know -- that's not been studied a lot, but nicotine, as such, I don't think we know anything about that, but it could have an active effect. Some of the other substances, I mean, acrolein, you know, we talked about that -- acro-lein or acra-lein, different pronunciations -- is an irritant, but it also stimulates the various cells to excrete various substances that can have a stimulatory effect on inflammation and could also have an effect on bacterial growth, I would think, so -- and I don't think it's going to take a lot of that. If a small amount of acrolein was in the airways, I think it could have an effect. I don't know; it's not been studied. But they clearly are -- that's an important area, I agree. And I think it's accessible for short-term studies as well. And there are even some, you know, in vitro studies that could be done there as well.

DR. DRESLER: Okay.

Okay, so here's one: Because colored and flavored e-cigs appeal to adolescents, are there specific health concerns, short- or long-term, to this population? From colored or

flavored e-cigs.

So Steve.

DR. HECHT: I think it's not just adolescents. The flavors, I think there are over 7,000, I read, different flavors being used in e-cigarettes, and this is totally unregulated. So I think this really needs to be looked at carefully, not only in terms of the toxicology, potential toxicology of the flavorants that are being used or the contaminants in them but also obviously the attractiveness of the product, particularly to children.

DR. ONCKEN: I was going to say I agree with that. I mean, that's one of the things that's sort of different about electronic cigarettes is the flavorings and the new -- besides having a potential for addiction potential, which I think is one issue. Is there any health effect? And when we've measured things -- I mean, it's not clear to me, for example, if somebody smokes an electronic cigarette and there are flavorings, does that just stay in the lungs, is it systemically absorbed, could that potentially have some effect? Can we measure that? I think that's a potential unknown area, and there could be risks that we don't know about.

DR. HECHT: These flavorants have not been evaluated in

the setting of inhalation. That could be extremely important.

DR. BENOWITZ: I think it's critical to get some dose data, because I try to figure how much of a particular flavoring chemical is in -- and I have no way of finding that out. And so some things will be present in trace amounts and some people in large amounts. I thought the comment that came up yesterday about diacetyl having higher concentrations in some cigarettes than e-cigarettes is a perfect example of that. And without having dose information, it would be hard to even figure out the toxicity questions.

In terms of health effects, again, the biggest health effect that I see in kids, in general, is infection risk. So when they get the flu, they get sicker. Or if they have asthma, maybe their asthma gets worse. So I think the acute respiratory effects are the things that we must be concerned -- but I don't know that they're linked to flavors at all.

DR. BAILEY: I presume different issues are being discussed about regulatory approaches and, you know, one thing -- as Neal said, if you don't know the details of what's there and how much of it, you really can't make much sense of it. But if the regulations required a reporting of exact amounts of various substances that were there, that would be good. Can

that happen?

DR. DRESLER: I'm not answering that question.

(Laughter.)

DR. BAILEY: Well, I mean you've asked me things I don't

know.

(Laughter.)

DR. DRESLER: I don't know that I say I don't know it, but

I don't know the answer to -- so do you know what? Let me --

so you said that it should be -- we should know the amounts.

Do you want to know the amounts in the liquid, or the amount

that comes out of however that product is designed?

DR. BAILEY: I think -- and that is different, but I think

what you really want --

DR. DRESLER: Your microphone. I'm sorry, I'm sorry.

DR. BAILEY: I'm from Alabama, you remember. I don't use

all these fancy things sometimes. Nevertheless, it's the

amount that comes out in the vapor that is important. But I

think we would like -- I mean, that is perhaps up to us to

figure that out because the experiments that are done depends

on voltage and all this, and it's very difficult to be sure

everything is reproduced. I think we at least need to know

what's -- how it starts, where it is there, and then perhaps

the scientific investigators could determine what comes out
after that.

DR. DRESLER: Any other comments?

I think I have one more question and -- okay. So how do
we define what is long-term e-cigarette use? So we've been
talking about short-term/long-term. We know kind of like
cigarettes, but how do you define what long-term e-cigarette
use is?

Microphone.

DR. BAILEY: I don't think we know. It hasn't been around
that long, so there's not been really any long-term e-cigarette
use in the sense of 30 years. When did it first come out, 5
years ago? Yeah, something plus or minus. So I think right
now 5 versus 1 month might be a way to do it now, but -- you
know.

DR. BENOWITZ: If I were going to define it, I would
define it in a disease-specific way. So I think after starting
at age 50 and you use it for 5 years, that might be long enough
to know if there are long-term harms. If you're 15, I don't
think you get any data about cardiovascular risk; you know, you
might with infection. If it's cancer, then long-term risk is
probably at least 20 years; long-term risk is probably 20

years. So to me, an operational definition, it should be

linked to the diseases you're looking for.

DR. DRESLER: Okay. How about for pregnancy?

DR. BENOWITZ: Pardon?

DR. ONCKEN: For pregnancy, it would be very short. Nine

months.

DR. DRESLER: Okay, all right. And then -- so do we have

Dr. Bullen?

(Off microphone response.)

DR. DRESLER: My red light is off. I had my back kind of

to it.

Okay, so thank you very much, panel. I have one last

question, but it's actually for Dr. Michele. So thank you very

much, panel. I'll ask her this last one.

This may be -- if cessation were assessed as a secondary

or exploratory endpoint in a clinical trial of an e-cigarette,

would this send the product down the CDER route as opposed to

CTP? So if cessation were assessed as a secondary or

exploratory endpoint in a clinical trial, would then the

product go down CDER or CTP?

DR. MICHELE: Right. So there have been an awful lot of

questions about when you require an IND, when you don't require

an IND. I'm not going to go there today because that's a

pretty extensive discussion. I will tell you that I encourage

everybody to come talk to the Division if you think you might

require an IND. We'll be happy to talk about your protocol

with you.

DR. DRESLER: Thank you.

Okay, then we're going to skip the break unless there's a

significant outcry against that, and we'll just go to the last

presentations. That means you get out earlier. So anybody

want to do the break now?

(No audible response.)

DR. DRESLER: Good for you. Thank you so very much.

Okay, so we'll move on to the next --

DR. LIMPERT: Good afternoon. My name is Jeannie Limpert,

and I'm a Medical Officer with CTP Office of Science. This

afternoon I look forward to providing a brief summary of the

Safety Reporting Portal and the adverse experiences that have

been reported to the Center for Tobacco Products. To provide

some background, CTP receives reports about tobacco products in

a number of ways. In January of 2014, CTP launched the Safety

Reporting Portal, which is a web-based reporting system

featuring tobacco product specific queries designed to

streamline and standardize some of this incoming information.

The goal of the Safety Reporting Portal is to identify

previously undetected health concerns and to take appropriate

action to prevent further adverse experiences and to educate

consumers about health risks. Reports submitted are reviewed,

evaluated, and where appropriate, issues will be addressed to

ensure the protection of the public health. Reports may be

about tobacco products currently regulated by FDA CTP, as well

as those that are not currently under CTP jurisdiction, such as

e-cigarettes.

This is a screen shot of the Safety Reporting Portal, and

you can get to it on the FDA CTP website. And the portal takes

the reporter through several screens designed to gather

information about both the tobacco product and the issue of

concern. And reporters can either register for an account or

they can submit their report anonymously.

This is a bar graph that represents the total number of

reports that have been received by CTP broken down by product

type. And as you can see, the total number of reports is

relatively low. The number of reports related to e-cigarettes

have increased the most in the last 2 years, and e-cigarettes

account for the majority of all reports received.

So what are some of the characteristics of the reports that we've received? Reports have come from e-cigarette users as well as non-users. Problems range from mild to more serious in severity. Reports have included both acute and chronic problems. Problems may be related to product function or defects. So some examples are e-cigarettes that have overheated and exploded, causing fires leading to burns and property destruction, concerns about contamination, unexpected smell or taste, and e-liquid leakage. We've received problems related to secondary exposures to aerosols, and we will address these concerns more in our upcoming e-cigarette workshop. Additionally, we've received reports about positive experiences that people have had with these products.

So what are some of the adverse experiences that have been reported? This table is not an exhaustive list, and it's not representative of all reports. Reports have included general symptoms such as feeling sick, flu-like symptoms, sleepiness; allergic reactions; eye symptoms including eye irritation and blurry vision; ear, nose, and throat complaints including hearing loss or throat sinusitis; cardiovascular issues including changes in heart rate, palpitations, chest pain; respiratory symptoms including shortness of breath, cough,

wheezing, sputum production, coughing up blood; GI complaints

including vomiting, diarrhea, and abdominal pain; neurologic

symptoms including seizures, headaches, confusion; and

dermatologic issues including burns, rashes, and sunburn-like

reactions.

So these reports provide important information about

potential health risks, but interpretation of the reports has

important limitations. Because reporting is voluntary, reports

received likely underestimate the true number and types of

adverse experiences associated with e-cigarettes. Data cannot

be used to calculate incidence or to estimate risk. And

experiences reported may not have a causal relationship to

product use. And the launch of the Safety Reporting Portal in

January of 2014 may have affected trends in reporting and

content.

Thank you.

(Applause.)

DR. DRESLER: Okay. Our next speaker is Dr. Israelski

from AbbVie Incorporated, speaking on the Role of Human Factors

Engineering in Medical Product Development.

DR. ISRAELSKI: Okay. Good afternoon. I'm with a

biopharmaceutical company called AbbVie that used to be Abbott,

and I'm in an area called Combination Product Development. And

listening to the talks here, I'm going to tell you about a

requirement to use human factors engineering, which I'll define

for those who don't know that, in medical product development.

And that includes drugs, biologics, devices, and what are now

called combination products, which are, as the word would

imply, a combination of a device and a drug.

     And I don't think there's anyone here from the Center for

Devices and Radiological Health, which is the device part of

the FDA, but what I've been hearing -- and I'm not a regulatory

expert; I'm just a company that gets regulated by the FDA and

others around the world. But if an e-cigarette device, it

could be a medical device because it directs -- it could direct

therapy, smoking cessation -- but if it delivers drugs of other

kinds that are therapeutic in nature, you could make the

argument that an e-cigarette is a combination product. And all

the things that I'm about to talk about in the next few slides

have to do with how you need to use human factors engineering

as part of that, and that's all about designing it for the user

so the user doesn't do things that could cause harm to them or

impact the efficacy of the mechanism of the device combination

product or drug.

So, first, I promised you to give a definition of human factors engineering. It's a field that's been around since World War II. It's not new, but it's been -- the expectations about it have been raised in the last few years by regulators around the world, including the FDA, United States. So it's taking data we know about human capabilities and limitations and applying it to the design of things, and it could be from space stations to toothbrushes, anything in between that a user interfaces with. And it uses the methods of the behavioral sciences to study people. We'll talk about some of those. And it also uses data that's been collected by applied psychologists over the years as part of that design process. And the whole point is to make products, medical products, which can be a drug, a device, or a combination of the two, safe, efficient, easy to learn, easy to use. "User-friendly" might be the term you've heard. "Ergonomics" is another popular synonym that gets at the same principle. "User-centered design," "human engineered," there are a lot synonyms.

My background, by the way, is I'm an engineer, and then I got my Ph.D. in applied psychology, and that's common for people who do human factors engineering to have a technology background and to know about the behavioral sciences. I know

very little about microbiology and medicine in that sense, other than applying the products that I work on to those purposes.

And we do human factors engineering in industry because of two things: Compliance with regulations from the FDA and elsewhere around the world, and there are standards in this area from ISO and IEC; I, personally, am very active in developing these international standards and also locally from the AAMI, the Association of Advancement of Medical Instrumentation -- the Association for the Advancement of Medical Instrumentation. There is also a strong business rationale for doing human factors engineering or usability engineering or any of the synonyms; products that are easy to use sell well. Think of Apple products. You have reduced development costs and support costs; products that are easy to use, easy to learn have fewer returns; people will buy more of them; they're faster and cheaper to develop because you get the right product done right the first time; you don't have to wait to make changes late in the development cycle where it's costly to do that; you have less liability exposure; lots of good business reasons. And that's why Amazon, Yahoo, Google all employ professional human factors people like me.

The features of human factors engineering that make it, we think, valuable is that it's systematic and scientific. It's not just common sense being applied to design, which is what has happened for a lot of products that we deal with where an engineer designs it for himself and they think, well, if I can use it, anybody can use it, and that would only be true if they were representative of the users. But when that's not the case, then you need to follow this process, that is, to point it out is, a regulated process for medical products. It uses methods of psychology to analyze behavior, try to do it rigorously, and it's practical, scalable, and is empirically based. We do things based on data, not simply a gut feel that something is easy to use or user friendly. And you can apply it to many things, as listed here.

This is a high-level view of the core methods of human factors engineering. So it starts off with -- you understand the context of use. We call that contextual inquiry; it's related to ethnography. You go out and you study people who are you going to develop this product for, and you understand who they are, the user profiles, their capabilities, limitations, understand the environment they're going to be using the product in, and very importantly, what are the tasks

they're going to do, because you're going to use this as the foundation for your design.

You have to re-document all this for the regulators, then you do early risk analysis, and that uses familiar tools to risk analysis; people like fault trees or failure modes and effect analysis. And the focus is the task that users do, and you're looking at early on which task, if done incorrectly, could cause harm or reduce the effectiveness of a medical product. And you use that as your foundation for design. You do a specification of the user interface, you set up some acceptance criteria, and then you do the hard work, you do the design, and that's usually early with simulations and prototypes, and you do testing. We call the early testing formative user ability testing, and with that, you're trying to give people tasks to do, and you observe how they do them in a controlled situation in a lab, and it's of people who are representative of the user profiles that you learned about up front in your contextual inquiry.

You try to stimulate the environment as much as you can. If it's low lighting conditions or a lot of background noise, your early formative tests would include that. And then you give people the tasks that are important to perform to get the

product use correctly. And, very importantly, the tasks that
have high risk associated with them from your early risk
analysis, that you're trying to design those risks out so that
you don't have to resort to weak forms of mitigation like
instructional materials or training, which are still useful,
but the best thing is you design the causes out. So you do
this early formative testing multiple times. You iterate the
design, you always find things you can improve, and you get to
a point where if you can't do any more that's practical, then
you do a final validation or a summative usability test at the
end using the acceptance criteria you set up in that user
interface specification.

I thought that was the pointer. Obviously, it wasn't. A
classic usability problem.

(Laughter.)

DR. ISRAELSKI: This is another way to look at the same
process in what's called the design control world. Medical
devices and combination products, which I told you are drugs
and medical devices combined, must follow a thing called design
controls, which is a way of rigorously showing how you
developed your product and documenting things so they can be
audited and reviewed by regulators.

So let's cross the top of the phases of development, that I think for many people would be pretty common sense. You have the concept phase, you do the design inputs, your design outputs, you verify, and you validate. These are meaningful terms to people in the product development world. And listed vertically are some of these human factors methods that I mentioned and a few more. So critical steps. Contextual inquiry: understand the tasks, the users and their environment, the risk analysis. You repeat the risk analysis many times during the course of development. It's an iterative process; you're never going to get the design done right the first time, and the FDA, in particular, wants to know about what did you learn in your formative steps, what modifications did you make to improve safety?

Usability testing is sort of one of the big hallmarks of what we do, but hopefully you could see, from my earlier slides, it's not the only thing. Some people think that's all human factors is, is just testing. You can't test quality, and you have to do all this up-front foundational work first. And then you have to do postmarket analysis for medical products, postmarket surveillance, because these early studies aren't done with huge sample sizes; that's not practical in human

factors studies. So the things may not show up in the early
evaluation, both the analytical ones or the empirically based
ones, usability testing. So you need to follow the product out
after it's released and look for -- and do some tracking and
trending.

As I mentioned, you have to document all these things, so
here's a task flow diagram that would document your task
analysis so you can show you really understand all the tasks
that the user has to do interfacing with your product. User
profiles, as I mentioned, have a lot of things about the users
that are very important to know because it will impact their
abilities to use the products if they have limitations, vision,
hearing limitations. You want to know something about their
measurements of body size; that's anthropometrics or strength,
that's biomechanics, very important design inputs.

You should document that in a simple way like a table.
The vertical columns are different types of user profiles; you
may have three or four. And the rows are elements of those
individuals, like hearing, vision, capabilities, and
limitations. The task environment or the use environment, very
important. I mentioned some of these things, like ambient
lighting, noise level. You want to understand all that. Are

they going to have to be wearing gloves, will they have eye

protection on? If they're using something like an e-cigarette,

will there be things that interfere with their use of it? And

then you also want to know about the social environment. Are

people doing this where they're stressed, are they calm, they

have many interruptions? These are all important things that

could impact safety.

You can document this also in the table form where the

columns are. This is an example of a medical device for

diagnostics. Each column is a different kind of laboratory,

and each row here are some elements that are important like

lighting, noise level, stress, chaos, et cetera.

Risk analysis. There's a standard for medical devices

from ISO 14971 that tells you about all the things you have to

do for risk analysis, and the whole point of this for medical

products is you have to think through originally, we call it a

cognitive walkthrough, a thought experiment, what could go

wrong? Brainstorm about that, document that in a failure modes

and effect analysis table -- you can have an example -- or in a

fault tree.

This is a graphical way of showing how events can be

logically added to each other through logic gates where things

could be added through an AND gate, which is a Boolean

operator, versus an OR gate. It has to do with how many

combinations lead to faults at the top of this tree. We're

trying to predict a use error that can result in harm.

Or a table format. And this is the one that most people

do or use, is a failure modes and effect analysis. So each row

is a task, and you're estimating the likelihood of a task being

done incorrectly; what's the severity, the harm. You combine

those two into what's called the risk level, and you prioritize

based on those that have the highest risk levels. Those are

the ones you're going to spend most of your time in design

trying to design out, so you reduce the possibility of an error

occurring that could have harm. And further on in the table

you'll look at methods of control, things you could do to the

design to try to reduce this likelihood of a use error

occurring, and what might be the effectiveness of that level of

control which you'd have to present data from a usability test

typically to show that this control actually does work.

Usability testing is this formal method where you

systematically observe people. Moderators are trained to do

this, to not bias people but to collect the data as if you were

a fly on the wall and the user was on their own. Usually we do

these as simulated use studies where no -- nothing is hooked up

to a patient, no active drug is being taken. There are

exceptions to that where it might be done in a clinical

environment, but you try to exhaust all the simulated use

studies beforehand.

    And as I mentioned, there are these formative studies that

can be done for lots of reasons, exploring early designs,

detecting if your usability goals are attainable. And then

there's the summative studies. Very small sample sizes, it's a

very qualitative exercise, unlike clinical studies or market

research because to run these usability studies is resource

intensive, very expensive. The regulators recognize that, so

they're not demanding very large sample sizes. This is not

something where you do inferential statistics and you have

confidence limits and Type 1, Type 2 error calculation. You're

basically looking for instances of use errors occurring that

could have significant impact on safety, and then your goal is

to do very deep root cause analysis to understand what impact

they're having and are there any more things you can do in

design to reduce them.

    And then there are quite a few references these slides

have in here for those -- I guess everybody can download these

later. They're available?

    (Off microphone response.)

    DR. ISRAELSKI: The webinar will be available. So you

will see there from the FDA, both the drug side of the house,

CDER, and the device side, CDRH, have guidances on human

factors engineering. Their expectations have raised

dramatically in the last couple years. And on the drug side,

in particular, they want to see studies done on packaging and

labeling, pill design or any of the things that impact how a

drug will be taken, and whether it might impact efficacy or

safety. The device side of the FDA has had human factors there

for over 20 years. They've issued guidances and updated them

recently. There are standards that I've shown here, and there

are some good websites that talk about human factors

engineering and how it can be applied to devices, drugs, and

combination products.

    Take home message: That it's focused on reducing risk

through a systematic process where you do this upfront user

research, make your design based on that. It's all risk based.

Each point along the way, you assess whether you've collected

data that would change your earlier estimates of the likelihood

of use errors occurring. By the way, I've been using this term

"use error." It's the term of art in human factors for medical

products these days instead of the common, everyday English

terms of "human error" or "user error." "Use error" is a

neutral term. It's not blaming the user. It's been in use by

all the regulators around the world for the last 10 years.

Because it says if something goes wrong when a user is

interacting with a product, we call that a "use error" because

we don't want to blame the user immediately, which was the

original thinking about this, that they're stupid, they don't

read the instructions, they didn't take the training, it's

their fault, we have a perfect product we designed. That's no

longer the thinking.

     The thinking is maybe your product has set people up, and

you can imagine maybe an e-cigarette could be designed in such

a way that you could mistakenly turn the voltage up and all of

a sudden create -- inhale contaminants at a higher level

because of a use error on the part of the user, so we don't

want to blame the user for not reading the instructions on

their e-cigarette. It may well be that the design has flaws in

it that need to be looked at.

     So said, risk analysis is very important. Iterative

design is a hallmark of this, and usability testing is one of

the cornerstones of human factors, but hopefully you've seen

that it's just a part of the whole process. And with that, I

think these are the slides I wanted to convey to you about how

human factors is another tool in this toolkit for designing

safe and effective products.

(Applause.)

DR. DRESLER: Are you ready for this? We think that we

have connectivity to Auckland, New Zealand.

So, thank you, Dr. Israelski. We will come back to that

session and clarifying questions, but first let's go to New

Zealand. And I believe we have his slides that we'll be

sharing.

UNIDENTIFIED SPEAKER: Chris, are you there?

DR. BULLEN: Yes, I am. Yes, sir.

UNIDENTIFIED SPEAKER: Okay, go ahead.

DR. DRESLER: Dr. Bullen, welcome to this -- we're

currently in our last session of our second day of the

e-cigarette. This is Carolyn Dresler. And so we will -- my

understanding is we'll be changing your slides as you say

"next," and so please go ahead. You're speaking both online

and to a room full of people. Please go ahead.

DR. BULLEN: And I can see that room full of people.

Thank you very much, Dr. Dresler, and hello, everybody. It's

about 7:15 in the morning tomorrow in Auckland, New Zealand.

So good to be part of this meeting, and I've enjoyed definitely

some of the presentations already. I'm going to be speaking

about the evidence for electronic cigarettes for smoking

cessation. And I'm a Professor of Public Health at the

University of Auckland.

Next slide.

And these are my -- if you could go to the next slide.

These are my conflicts of interest declarations. And my fellow

-- my background in tobacco control research. And I have been

a principal investigator of several electronic cigarette

studies. I have no affiliation with the tobacco industry, nor

have I received any benefits from manufacturers or retailers of

electronic cigarettes.

So I just want to acknowledge -- next slide -- my

collaborators on the recent Cochrane Review: Dr. Hayden

McRobbie, Jamie Hartmann-Boyce, and Professor Peter Hajek, all

in the UK. And so what I'm going to be presenting, the

findings from the recently published Cochrane Review.

Next slide.

So just very briefly, my introduction to electronic

cigarettes occurred about 6 or 7 years ago when a colleague

introduced me to these products, at which phase they were

almost unheard of. But they were an interesting phenomenon,

and we decided to test and see if the claims being made from

Chinese distributors could be validated in the lab setting.

And so we did a small portion of the trial looking at changing

craving and withdrawal syndromes and nicotine absorption

following use of an e-cigarette comparing with a nicotine

inhaler and normal cigarette smoking. And we found that the

electronic cigarette was about as effective as a nicotine

inhalator at withdrawal and craving reduction. And, however,

nicotine delivery was very poor compared to normal cigarette

smoke.

     Next slide.

     So we undertook a Cochrane review last year. This is an

attempt, a systematic attempt, to gather all the available data

and, where possible, to pool that data to gain statistical

power, to make some judgment around the efficacy of particular

interventions. So this is just a shot of the front page of the

Cochrane review.

     Next slide.

     The aims of the review were -- there are several, but the

primary objective was to evaluate the efficacy of electronic cigarettes for helping people who smoke to achieve long-term abstinence. We had some secondary objectives around smoking reduction and adverse effects, but we haven't got time to go into that. But you can find the review on the Cochrane Collaboration Tobacco Addiction Group.

Next slide.

So in terms of assessing efficacy of electronic cigarettes, I'm sure you've all heard how difficult this can be. These products are a wide range of brands and models constantly changing and evolving. However, in common, they all vaporize propylene glycol and glycerol as a carriage medium for nicotine and flavors. But those constituents differ quite widely from product to product. And even within product line, the range of strengths of nicotine, for example, vary according to -- vary from the labeling. But in early 2014, one study suggested there were well over 7,000 unique flavors, and I'm sure there are a lot more since. The other aspect of electronic cigarettes is the user experience. We just heard about human interface with products, how important the user experience is in terms of what comes out the other end of the product.

And the next slide.

Just show you six studies on different brands of e-cigarettes showing how nicotine delivery varies by brand, and these are some of the common ones you're going to find in various markets.

And here, showing the next slide, the variation with models. And you're probably aware that there have been several generations of e-cigarettes, so the first e-cigarettes that were trialed were what we call the first generation, generally looked very similar to cigarettes; the second generation were the cartomizers; and third generation, if you like, were becoming more sophisticated looking, less and less like a typical cigarette, with large battery packs and large reservoirs for holding e-liquid.

Next slide.

We turn to the types of studies, participants, and the interventions that we looked at in our systematic review. We looked at all randomized controlled trials that had recruited smokers who were randomized. Electronic cigarettes were a control condition and which could either be a nicotine-containing product or a placebo product. And the abstinence rates were measured, had to be measured at 6 months or longer.

And we also looked at cohort follow-up studies that were done for 6 months or longer. Again, all the participants had to be current smokers, but in some of the studies, some of the smokers didn't want to quit smoking, and in some of the studies, people were keen to quit smoking. Again, the interventions looked at the comparison between e-cigarette versus alternative smoking cessation aids, including NRT or no intervention whatsoever; nicotine-containing versus no-nicotine containing e-cigarettes; and we looked at e-cigarettes plus standard smoking cessation, behavioral or pharmacological support, versus standard treatment alone.

Next slide.

So this slide just looks at the outcome measures that we considered. So we looked at cessation at the longest follow-up point, at least 6 months, using to intention to treat analysis, the strictest definition of abstinence, and we preferred studies that had biochemically validated self-reported abstinence. Just to move on in the interest of time. But the secondary outcomes just relate to adverse events and smoking reduction.

So, in terms of search methods, just standard search terms using only major scientific literature databases, including the

Cochrane Central Register of Controlled Trials and the Tobacco

Addiction Group's Specialized Register, using those search

terms there. And we also searched some other sources, so there

are reference lists of studies found in the literature and the

metaRegister of Controlled Trials database. And we also

contacted the authors of known trials and other published

e-cigarette studies in order to try to mop up as many of the

studies that were out there as possible.

Next slide.

The methods. We searched for titles and abstracts and

prescreened those. Two reviewers prescreened those and then

extracted the data in a systematic fashion from all the

included studies, and one reviewer did that, and the other

checked if that was an accurate process.

We also undertook a risk of bias assessment, and that

looks at seven domains, such as random sequence generation,

allocation concealment, blinding, incomplete outcome data,

selective outcome reporting, and other sources of bias. And

then you assigned a grade, a risk of bias, to each of those

domains. This is following the method used by the Cochrane

Review and is articulated in the *Handbook for Systematic*

Reviews method.

Next slide.

We also looked at a different range of measures of treatment effect, so dichotomous data analyzed by calculating the risk ratio. We also did the same thing for cessation and levels of carbon monoxide in expired breath. We calculated 95% confidence intervals around the relative risk, risk ratio estimates. We used only RCTs where individuals were the units of randomization; in other words, we excluded cluster randomized trials. In fact, we didn't come across any clustering in those trials. And we summarized the data from the cohort studies in a narrative fashion.

There's a lot of missing data in some of these studies, so we treated participants with missing data in a conservative fashion by counting them as still smoking. We assessed heterogeneity in the usual statistical fashion calculating I^2 statistics, and if the I^2 was greater than 50%, we had evidence of substantial heterogeneity between the different studies.

So next slide.

Data synthesis. So as I said, we attempted the narrative summary of the included studies, and then where it was appropriate to do so, we pooled the data in the meta-analyses, and using a fixed-effect Mantel-Haenszel model to calculate the

risk, the relative risk with 95% confidence intervals.

Move on to the next slide.

Search results. We found 589 non-duplicate records through database searching and another 5 records identified through other sources, so a total of 594 papers were screened. We were able to exclude 526 quite quickly on the basis of our pre-existing selection criteria. Sixty-eight full-text articles were assessed; we excluded 39 as they didn't meet the inclusion criteria. At least 29 records, and some were of studies that were still ongoing, so at the end of the day, it came down to 2 randomized controlled trials, 10 prospective cohort studies, and 1 retrospective study. And in terms of meta-analysis, we only had the 2 randomized controlled trials to include in the meta-analysis.

The next slide.

So the excluded studies were excluded mostly because they used e-cigarettes for less than a week or gave no information about cessation, reduction, or adverse events. And we excluded all cross-sectional studies or any that had a very unclear definition of use, such as any use in the last 30 days. And a couple of the longitudinal studies we came across were excluded, as well, because some of them included data that was

only collected at follow-up or didn't report on changes in smoking behavior.

So the published randomized controlled trials, these are summarized in the table. The slide shows the Caponnetto study published in 2013 and a study that I led published in the *Lancet* in 2013. Different populations; the Caponnetto study, smokers were unmotivated to quit, whereas in our study, they were motivated to quit. Very similar inclusion criteria, different brands of e-cigarettes. Both were what we would call first generation e-cigarettes, and I'll talk about them in a moment. The sample size was doubled in our study, 657; 300 participants in the Caponnetto study. The Caponnetto study had an interesting way -- of delivering intervention in that they offered a reducing level of nicotine in e-cigarettes. We provided -- had a three-arm study of 16 mg e-cigarettes, comparing it with patches and also placebo. The Caponnetto had no normal treatment comparator. Neither study offered much in the way of behavioral support, and that was intentional to replicate the environment under which most e-cigarette users find themselves. In other words, they purchase these products online or go to a vaping store, and they don't give you any counseling to quit along the way. The intervention periods

were very similar, and both studies ran about 3 months.

Follow-up in the Caponnetto study are a year, 6 months in the

New Zealand study. Both had similar statistical power and

verified continuous abstinence at 6 months for the primary

outcome. So that's it in a nutshell, and I'll just jump to the

next slide.

This is the Caponnetto study. It was called the ECLAT

trial published in *PLOS ONE*.

Next slide.

Here's the study design, these three arms, different

regimes: one group with 7.2 mg nicotine continuing through

intervention phase; another group stepping down to 5.4 from

7.2; and a placebo arm.

And then this shows the results on the next slide,

validated abstinence at 24 weeks. So we're looking at the

6-month results, which is what we included in the meta-

analysis, with quit rates around 12% in the 7.2 mg group;

stepped down, 10%; and the next group, which stepped down to 5%

in the placebo arm. Very small numbers, low levels of

cessation.

So the strengths and limitations -- next slide -- of the

ECLAT trial was that it was an early exploratory trial, it was

double-blinded and had a long-term follow up. And it was a

pragmatic trial in that it attempted to replicate the real

world environment. However, there were a number of

limitations, and I won't go through those in detail, but one of

the key limitations was the unreliability of the product and

the low nicotine content of the e-liquid, high loss to follow-

up.

Next slide.

Our trial, run pretty much at the same time and published

just a few months after, conducted in the New Zealand setting.

Next slide.

Our design was a three-arm trial and compared a 16 mg

e-cigarette with a placebo cigarette in a blinded fashion, and

we had a usual care comparator, which was the 21 mg patch,

which is widely prescribed in New Zealand through our quit

smoking services as a first-line treatment for smoking

cessation in smokers. And, again, the population was different

from the Caponnetto study; ours were all people who had

expressed an interest in quitting. And you can just see, at

the bottom of that slide, at 6 months we had just somewhat of a

differential follow-up, lower in the e-cigarette treatment arm

as compared to the 21 mg patch arm.

These are the baseline characteristics -- next slide. So we had the typical group of smokers. We had more women in the study than men, but they were around in the early '40s, well educated, smoked about 18 cigarettes a day, and some of the Fagerstrom scores around about 5.5, 5.6 across all arms.

Next slide.

We found, at 6 months, in terms of continuous abstinence, i.e., no more than 5 puffs over a 6-month period verified by carbon monoxide testing, that the results were not that different between e-cigarettes and the patches, 7.3% quit rate and 5.8 in the patches group. And using 7-day point prevalence, they were much higher, 21% versus 15.6%.

And when we undertook a non-inferiority analysis, just looking and asking the question were e-cigarettes at least as good as nicotine patches, in the first session, we found that they were non-inferior. In other words, we could say, with some degree of confidence, that nicotine e-cigarettes delivered the same sort of cessation results as a nicotine patch.

Next slide.

This shows the comparison between the 16 mg e-cigarette and the 0 mg e-cigarette, and you can see there's a difference. But, again, it's not that great: 7.3% versus 4.1%. In the 6

month continuous abstinence outcome, really no difference in
the point prevalence outcome.

Next slide.

So a number of strengths and limitations to our study. It
was the largest study conducted to date, pragmatic design,
focus on sustained abstinence. And our quit rate was similar
to that seen in NRT trials with limited behavioral support, but
it was lacking in power. We didn't really know on what basis
to power the study, so it was a guess, an educated guess. We
also had low nicotine content e-liquid, and we found out, of
course, later on, during the trial, that we had an unreliable
product. And differential drop-out as well.

So, pulling that together, in terms of the Cochrane
Review, there was really only one study to look at, comparison
between nicotine e-cigarettes versus NRT, and that was our
study, and that's the forest plot showing the fit and the
diamond. And just to the right of that little, the blue box,
just to the right of the narrow fit side of the line, relative
risk 1.26, and the confidence interval is straddling that
narrow fit line. But as I said, in the non-inferiority
analysis, we could say perhaps that there is no difference at
least in our study with the nicotine e-cigarettes and NRT

patches.

Now, this is probably the most interesting slide in my presentation, the next slide. It shows nicotine versus non-nicotine e-cigarettes. And when you pool the results between the two randomized controlled trials, what we find is that we do get an overall effect of nicotine compared with non-nicotine e-cigarettes, and the relative risk is 2.29, and the confidence interval shows it is statistically significant. The I^2 showed no significant statistical heterogeneity between the two studies. So take-home message: If you add nicotine to e-cigarettes, they're more likely to help you quit than non-nicotine e-cigarettes. And this is an important issue in my country where it's only non-nicotine e-cigarettes that are legally allowed to be sold. You can import nicotine for personal use, but you can't sell nicotine containing e-cigarettes. So nicotine does seem to make a difference.

Next slide.

The cohort study in terms of cessation. These are the cohort studies that were included, and there was a mix of motivated and unmotivated smokers in these studies. Most of the people were using electronic cigarettes that contain nicotine. And you can see the 6 months, 12 months, and there

were some 24 month outcomes, and they were a bit of a mixed

bunch. But I think it's important to look at the risk of bias

assessment table, and this is on the next slide, which looks

like a game board of some sort, but the green circles represent

sort of a checked state, that they were low risk of bias. You

can see the two trials. Most of these bias domains were

actually low, whereas with the cohort studies, obviously there

was no random sequence generation, no allocation concealment,

and in most of them there was no blinding appearing. So the

bias was much higher in those studies.

So the next slide, just in conclusion. There is limited

data from one randomized controlled trial to date that nicotine

containing e-cigarettes give similar quit rates at 6 months as

NRT, that smokers who used nicotine e-cigarettes were

significantly more likely to stop smoking than smokers using

placebo e-cigarettes. However, the effect size, the absolute

effect size is very small, a 5% difference between both for the

nicotine versus non-nicotine e-cigarettes. But perhaps that's

not unexpected given the low level of behavioral support

offered to the people participating in these trials.

And just -- the next slide suggests there were a few

caveats around over-interpreting these results. Firstly, while

both trials were well conducted and judged to be at low risk of

bias, the quality of evidence overall is relatively low because

we don't have many trials. We only had two, and that's not

good. And both used poor-performing products, which were the

only products available at that stage when the trials were

embarked upon. And both trials, being relatively of

exploratory nature, were underpowered from a statistical

perspective.

So next slide.

So the strength of the data that I presented to you today

is that it really is the first systematic review that's pooled

the data and conducted a meta-analysis. However, there was one

other effort to do this, which was made by Rachel Grana and

colleagues and provided a lot of information to the World

Health Organization assessment of e-cigarettes that was then

published last year. Our findings differ with those results,

but our findings do align with some data that's emerged from

the UK and published by Jenny Brown and colleagues, which is

from a large representative population. So I just want to very

briefly reflect on those.

The differences -- next slide is the WHO review. We

excluded three of the studies that were included in the WHO

review, and I think that's made a difference. We did, however,

include Grana and Choi 2014 studies in our review, which

neither detected a difference between smoking cessation in

smokers that did or did not use e-cigarettes at baseline. Both

of those studies were limited by the definition of e-cigarettes

used at baseline. So we think we've been pretty robust in the

way we treated the different studies, and we feel there is a

justification for the way we excluded the studies that were

included in the WHO review.

And then just moving -- next slide -- to the Brown study

on the real-world effectiveness from the UK data. They had

wonderful data on the stop smoking services and have --

studied, pulling up 5,863 adults who had smoked from the

previous year and made at least one quit attempt in that period

with either an e-cigarette or NRT bought over the counter or no

aid in their most recent quit attempt. So you can see there's

a significant difference between self-reported abstinence in

e-cigarette users, those who quit just over the counter,

nicotine replacement therapy, and then between e-cigarette

users and those who quit cold turkey, if you like. So relative

risk or odds ratio, 1.63 comparing e-cigarette and OTC NRT.

And the UK continues to get very interesting data on the

number of smokers who are using e-cigarettes for smoking

cessation. This is taken from smokinginengland statistics, the

latest information to hand, and you can see the large numbers

in green of people using electronic cigarettes compared to the

numbers declining of people purchasing NRT over the counter and

the numbers of people having NRT prescribed to them through

stop smoking services in the red line.

Next slide.

And just some more data from Jenny Brown's work in the UK

from -- study suggesting that perhaps 20,000 additional ex-

smokers have resulted from the use of e-cigarettes, the growth

of the e-cigarettes and the effectiveness at a population

level, it appears, from these data collected in the UK.

Next slide.

So I think there's a lot more that needs to be done. I

know work is underway with further randomized controlled trials

looking at efficacy. I'm sure the designs will be better than

those that were initially undertaken. We know a lot more about

these products. We need to use more reliable high-quality

devices such as the Generation 2 devices. We need more

statistical power, and we need to try and aim for longer-term

follow-up and collect detailed adverse event data, and be sure

to try and validate self-reported abstinence.

There are these trials going on -- next slide -- a lot of trials registered, but unfortunately, a number of them seem to be quite small, but there will be an opportunity to include these studies when they have their outcomes in any future meta-analysis.

And that's it for me. I hope it's been of interest, and I'm sorry I haven't been present to make my presentation a little more dynamic. Thank you very much.

DR. DRESLER: Thank you, Dr. Bullen.

Let's take some questions if we have any questions for him. So I know this is perhaps last minute for you, so if you have any questions, can you jot them down, raise your hand? I'll come over.

Perfectly clear, answered all your questions about cessation in e-cigarettes? That's what I'm seeing.

Hold on one second, Dr. Bullen. I think we will be getting one question.

Thank you very much, Dr. Bullen, for doing this for us --

(Pause.)

DR. DRESLER: I think they're going to be long questions, Dr. Bullen. Hold on a sec.

(Pause.)

DR. DRESLER: So, Dr. Bullen, is a randomized clinical

trial the best study design -- okay, let me start again. Is a

randomized clinical trial the best study design for an open

population for a behavior like e-cigarettes?

DR. BULLEN: Okay. Well, I think there's no question that

when we are trying to test the efficacy and safety of a novel

product, there is no question that a randomized controlled

trial is the optimal design. However, if we're trying to ask

the question, can electronic cigarettes in an ideal world help

people to quit smoking, we might want to do what Thomas

Eissenberg and colleagues are doing and find if you like an

optimal product and test people in a relatively controlled

setting.

I'm quite interested in what you described as more of an

open sort of design, but still using randomization, because

without randomization, we run into the problem of bias and

confounding, and we're always going to be asking the question,

could there have been some unmeasured confounding factor that

distorted the results that we see? There are different ways of

randomizing, and in an open real-world environment, there are

some options besides the standard randomized clinical trial

design, such as a stepped wedge design or cluster randomized

trial where perhaps the units of randomization could be a

treatment center. These all have their own design problems.

At the end of the day, we're trying to find the truth,

clear of any distortion from various sources of bias. So I

think we should strive to undertake a bigger, larger, longer,

more well-conducted randomized controlled trials so that we can

compare the results with the gold standard treatments that are

currently out there. I think that's an important comparison

that needs to be made.

But we also need those more open studies. Some of them

are not going to be randomized studies, like the UK data, where

we're looking at a population of what is the impact of the

introduction of these new products on populations. And I think

that's showing, I feel like, another side of the coin. And

then really, there's a judgment call that has to be made. But

from the regulatory perspective, I don't think there's any

question randomized controlled trials are the benchmark that

have to be followed. And so if regulators wanted to consider

whether products like electronic cigarettes should be on the

market in some way, shape, or form in a more regulated fashion,

then the manufacturers and retailers are going to have to come

up with randomized controlled trial data. There is robust --
that appears with placebos, appears with standard treatment,
and follows people out long enough to identify any major early
stage adverse effects that might be of concern.

DR. DRESLER: Okay. So here's another question that I
know you're familiar with the topic. Hasn't it been shown that
success depends on other factors such as support? So I'm
thinking the person must mean it's not so much the nicotine;
you were saying there's a difference between nicotine
containing e-cigarettes and nicotine -- non-nicotine and
nicotine e-cigarettes. So isn't success just dependent upon
other factors such as support?

DR. BULLEN: Yes. Of course, behavioral support is an
important additive factor in both the trials that we included
in the meta-analysis. Neither had much support. They offered
some support available to people who wanted it, but -- and
equivalent proportions in the different study arms availed
themselves of that support. But it wasn't part of the
intervention, if you like. And this was intentional, in our
study anyway, because as I said earlier, we wanted to replicate
the real world environment that most e-cigarette users find
themselves.

Now, there will be some who attend a clinic, and the clinician says, well, you've tried everything, have you thought about e-cigarettes and provides some behavioral counseling in that setting. But for most e-cigarette users, they're purchasing them in the store or online; they have no behavioral support whatsoever. So that's the rationale for the two randomized controlled trials included in the Cochrane Review.

But you're right. If you did add behavioral support, and I think this is an important research question, what incremental benefit would we be likely to see? And if we imagine that electronic cigarettes are really another form of nicotine replacement therapy, then just like the nicotine replacement therapy trials that include behavioral support, we are likely to see enhanced quitting rates as a result of that behavioral support provided to people.

DR. DRESLER: Okay, thank you very much. Those are the questions that we had. So, again, thank you, Dr. Bullen, for giving this presentation and being patient with us as we get it broadcast. And also everybody in the room, thank you for that patience. So I think we'll sign off now from Dr. Bullen and we'll go back and -- okay. So we have one last --

(Applause.)

DR. DRESLER: Thank you.

Okay, so our last presenter before we go to the clarifying questions will be Dr. Stansbury, who is from the FDA Center for Drug Evaluation and Research, CDER, and he will be speaking on Product Labeling and Consumer Labeling Comprehension.

DR. STANSBURY: All right, I'll make this short, and then we can go home.

Okay, I'm Jim Stansbury. I work with the Division of Nonprescription Drug Products at the Center for Drug Evaluation and Research. I have no conflicts of interest, and I have no particular regulatory skin in the game at this point, not being with the Center for Tobacco Products. However, this might make a difference if Dr. Bullen's very fine and promising information might be brought to us for the approval of a cessation product.

Okay, so what I'm going to do is I'm going to contrast some objectives, try and compare a little bit with how our thinking is in the Center for Drug Evaluation and Research with the regulation of tobacco products, and then talk about four kinds of studies: label comprehension, self-selection, actual use, and human factors, which I won't have much to say about given Dr. Israelski's fine presentation.

So the point of consumer studies, when you're talking about drugs, is about safety and effectiveness. Keep that paradigm in mind. Once again, that's the framework, that's the world view we're taking when we go to approve a drug, so -- or a therapeutic device. We want to demonstrate consumers can use it, that the label is effective as a tool in risk communication, that consumers begin to make the right choice about selecting this, and this implies a different kind of study. Safe use of the product, for example, an actual behavioral -- in other words, we shift from risk communication to actual behavior. And, indeed, human factors usability studies, which is what we tend to look at, that last product in the human factors continuum is an issue of behavior and interaction.

And if we think about the consumer studies being applied -- and once again, this is a projection, this is speculative on my part. If we're thinking about how you might go forward with these kinds of studies, looking at something that's going to be regulated as a tobacco product, then it changes a bit. We're interested in risk management and risk mitigation. I can promise you, we're very, very unlikely to consider these products safe and effective and use that framework for them.

So we want to know if the label effectively communicates risk, if there's "relevant warnings, precautions, side effects, and contraindications," language right from the Tobacco Control Act. Consumers can decide against use of the product based on the labeled information. Again, consumers use the product as directed, taking a focus on misuse and overuse. And, finally, can consumers use the device in a way that doesn't aggravate the existing risks, okay. This would be the concern of a human factors format.

Now, this is unless -- and this is a big "unless" -- unless the e-cigarette were to be developed for a therapeutic purpose such as smoking cessation, and in this case it would, in fact. As Dr. Michele pointed out earlier, a drug-device combination with a drug primary mode of action. Okay, so it changes the framework, doesn't it? It's a whole different paradigm. And, in fact, these consumer studies, as we evaluate them, would be a bit different.

I've taken this slide from Dr. Michele that shows, once again, the types of consumer studies that we consider in the Division of Nonprescription Drug Products: label comprehension, again, understanding, comprehension; self-selection, choosing; actual use; and human factors.

So, typically, label comprehension studies, as we evaluate them for the approval of an over-the-counter drug product, involves a test of risk communication. We've mentioned that sometimes and in fact in our guidance these are referred to as trials. Well, you know what? They're not really trials; they're tests. And I promise you, this is not rocket science, these tests. And, in fact, they tend to be quite simple for response, and they're open label and controlled tests. So when we think about risk communication, it's a three-finger exercise, right? This is not too hard, right? So what have we got in risk communication? We've got a content, the content of the message. We've got the accessibility, that is, people's ability to access that information. And then we've got comprehensibility, understanding. Can we form a complete thought around this and act on it, right?

Now, the study you see acted out here, this is probably a behavioral study. Johnny is trying to get through the door. But, actually, in a label comprehensive study framework, we might ask, "Johnny has read the sign on the door. What should he do if he wishes to enter the building?" Okay. So this might be the type of question we ask.

Now, scoring tends in these kinds of tests to be focused

on each communication objective. We establish these

communications really on the primary risks that get found in

the label, okay. So what's a label going to look like? Let's

imagine a future, shall we? Let's imagine a product that has

this label: If you do not use; if you continue to smoke; if

you're pregnant; if you have diabetes; if you have a known

allergy to nicotine, propylene glycol, or glycerol -- so we can

imagine this is part of the label. These may be the key risks,

then, that we wish to see and see as the primary communications

objectives, right? These can be addressed as scenario

questions, and oftentimes they're scored, they're scored with a

priori thresholds. These are simply proportions, okay.

The method for scoring tends to be a 90% success rate.

That sounds excessive, but let's suggest this is an open-book

test. You've got the label in hand, you're being asked about

it, the probability of success kind of ought to be 1, you know,

if you can look at the label and answer the question. But

we're human, so there went 10% of our response and frankly

oftentimes 20% because we tend to make a hash out of things.

We're not asking for perfection, but certainly we would like to

know is this risk communication interaction with people working

well, right? And so when we start to see those levels fall

below 80% and really down, well down below the Lake Woebegone threshold of 70%, you know, we know that there might be something wrong with this risk communication. Dr. Israelski suggested about the devices, the imperfections may not lie with the persons but rather with the communication. So sometimes when we want some rigor, we measure the lower 95% confidence interval, and we are very interested in having representative samples.

I started my career at FDA with the Division of Risk Management, and oftentimes we would see a sample from time to time that was composed of 80% college educated women of European descent from Maryland and Pennsylvania, okay? This might not be a good representation of the United States population, okay? But we don't always set quotas, we haven't been hard about this, but indeed we would like to see strong representation by respondents who are, in fact, of low literacy, which may be as many as 30% of us, low health literacy, that is, and this is generally based on a REALM health reading test and a figure that comes to us from the National Academy's publications on the topic.

These studies are typically designed very simply; they're often all-comers, convenience samples. Somebody mentioned

yesterday or this morning that marketing experts could conduct

studies, indeed, that we find that sometimes these kinds of

studies are conducted by competent marketing firms. They tend

to go to shopping malls and intercept people to read the label

and test them out. But, indeed, there is a need to purposively

augment the sample sometimes with low literate respondents,

okay?

So this is how we test risk communications at the most

fundamental level. But we can up the game a little, and this

is what happens with what's called the self-selection study,

the second type of communication study. It's best thought of

as a higher-stakes label comprehension test in that the

individual endpoint is the ability to correctly select the

appropriateness of using the product based on an individual's

characteristics. It's a simple dichotomous outcome, all right.

It ought to be a yes or no. So after reading the label, the

consumer is asked, you know, should they use this product, are

there contraindications that suggest that they shouldn't?

Now, how can the stakes be higher if it's just really

about one question? Well, as it turns out, sometimes the whole

approval of a drug, of a drug product can, in fact, hinge on

the self-selection. This was, it was well publicized, well

covered in the literature. For example, statins, when they --

the first attempts at approval of an over-the-counter statin,

Mevacor, in about 2005, a series of articles came out, you

know, suggesting that really self-selection is the problem. So

it is a communications objective and the ability to self-

diagnose and see if this product can be used without a learned

intermediary, right? A pharmacist or a physician. And it has

high importance, indeed, for first-in-class drugs.

These tend to be all-comers designs as well. But unlike

the labeling studies, it may be useful at times to augment the

studies to enrich them. The outcome is often the proportion of

the appropriate self-selectors. More importantly, the

de-selectors.

So it's really important to get these outcomes right in

self-selection studies, and it's sometimes problematic. Many

of you -- how many are epidemiologists out here or have some

background in epidemiology? Probably just everybody. Okay.

Well, if you don't, you probably will before it's all over.

This is the old truth table, a 2 x 2 table with categories A,

B, C, and D. Or in other words, if a drug is selected by a

consumer as okay, and indeed, that selection is appropriate,

this is a true positive response, okay. And you can go through

this table.

You have false positive responses, which are problematic,
right? That's a worry, right? Well, false negatives, no, it's
not okay for me, but indeed, the drug is appropriate, is that a
big worry? For manufacturers, sometimes. They tend to think
it's a lost opportunity, right, to use their product. For us,
not so much. But it's not so much a safety consideration. But
when it's not okay for me and when it's inappropriate, that's
real important to know that people are making the right
decisions. I have diabetes, I may be subject to hypertension;
it may not be good for me to use a nicotine product, assuming
that we've got the body of evidence to be able to label in that
way. I'm being purely hypothetical here, okay.

So picking the right outcome is very, very important.
Oftentimes our sponsors, our developers sometimes want a broad
outcome that suggests well, if they get the right answer,
that's good. But the denominators, as you always know, matter
and sometimes we're really interested in this right side of the
diagram where things are inappropriate. So if a company is
bringing a tobacco cessation product to us with therapeutic
value to be treated as a drug, we're apt to be very concerned
who shouldn't be using it. In other words, we want to mitigate

that risk a bit.

Actual use studies are actual behavioral studies. They
are not clinical trials, so they are cohort studies; but they
are a chance to use the product. As such, they are clinical
studies that involve the use of the drug under consideration.
They are categorized as consumer studies, but they're a bit
naturalistic, not so much in terms of observation, but indeed
day-to-day use, which is then in turn self-reported. We have
heard a lot during the course of these 2 days about the
challenges and weaknesses of self-report. And, in fact, we
begin to ask people, and we're getting a little bit better and
a little more exacting about asking for diary information that
may be electronic rather old-fashioned paper diaries, which
aren't so good. Okay.

Individual outcomes are often instances of inappropriate
use. The parameter of interest, again, may be the rate or
proportion of misuse in the population. And, in fact, there's
been some recent interest in the application of trials in
actual use studies. That changes the question, doesn't it? Is
the question something that we can derive from a cohort study;
that is to say, we watch people use the drug and we want to
look at instances of misuse and account for that. And that may

be good enough in many cases.

In other cases, we want to introduce some rigor. Is the
use or misuse of this product no worse than an existing product
on the market? That's a non-inferiority trial. I know
Dr. Bullen talked about this. And moving on just to digress a
moment, non-inferiority may be a very strong way to approach
the whole question of efficacy trials. Let me just throw that
out there. There was some concern yesterday about are clinical
trials the right mechanism, and the question to that effect
today, right? But, indeed, if we think of non-inferiority, a
comparison against existing tobacco control products or
cessation products, NRT, who knows? This needs to be
discussed. Recent interest in application of trials, then,
have moved somewhat.

Human factor studies. A lot was said. We look at the
usability studies. In general, we're just interested in what
happens at the end of the day. They can generally be conducted
with a novel device or a form of delivery. This is often a
simulated situation in these actual use trials, and of course,
they've got a great deal of formative research underlying them,
we assume, and we like to see that that has, in fact, been
carried out. But they don't involve such big samples, but

indeed involve a great deal of rigor and a bit of engineering, okay? These can be very important for e-cigarettes.

So by way of conclusion. Let's get out of here. Our interpretations of results sometimes differ from a sponsor's. We're not always in agreement, and we're sometimes not in agreement over the same body of evidence. Sometimes the glass is half full. We have good advocates come in for sponsors sometimes who are quite sanguine about how well things worked out. Others of us would see a glass that's half empty. I often order a cheeseburger if I saw a need for a different kind of study, okay.

But our key findings should involve an understanding of why consumers get it wrong when they do get it wrong, all right? This is something we like to see, and this suggests another component to many of these studies that we don't see enough of. Occasionally we need to measure something, some count of mechanics, but we had some good examples of qualitative research earlier today, and mixing methods can be a very valuable strategy, in fact, to gaining a greater understanding and, indeed, finding a path forward, how a product might come to market in a better way.

So there are some fundamental differences between OTC

drugs and tobacco products, obviously, which may imply some

differences in consumer studies, unless, of course, they're

brought in under an IND as a therapeutic drug. There seem to

be commonalities, and hopefully, some of these models can be of

use across an array of types of studies. Objectives and key

questions should drive the methods.

This is true in research more generally, but it oftentimes

gets forgotten when there's some urge for the methodological

tail to wag the conceptual dog, right? And sometimes there's

just more than one good way to do things. Oftentimes there are

many ways to do things poorly, I'm afraid, but hopefully

there's more than one path to success. Don't be afraid of

methodological innovation, and don't be afraid to be a

methodological overachiever, especially with behavioral

studies.

Thanks.

(Applause.)

DR. DRESLER: Thank you very much and let's -- clarifying

questions or how about non-clarifying questions for either of

our last two speakers in particular? Thank you. I'm sorry,

last three speakers.

Dr. Limpert, FDA adverse events available online, will FDA

be updating the reports for the remainder of 2014 through early

2015? Currently, the last report is from March 2014, and if

yes, when?

DR. LIMPERT: So we do plan to put the e-cigarette adverse

experience reports online, but we do not yet have a definitive

date.

DR. DRESLER: Is that because it's related to deeming or

anything like that? No, don't think so. Okay.

Okay, who's --

No more questions? No?

Okay. Well, thank you very much to the speakers for

speaking yesterday and today, and then to the audience and for

all the questions and making it such an interesting 2 days. So

thank you very much, and actually, what I have here, I have an

ending bell.

(Bell rings.)

DR. DRESLER: It's like the closing bell for the stock

market, you know, on an up day or something.

(Applause.)

DR. DRESLER: So we have a closing bell. Thank you all

very much. Just to remind everybody that this will be online.

It was recorded and a transcript, and so as soon as that's

available, it does go online. That was a question earlier too.

(Whereupon, at 3:10 p.m., the meeting was concluded.)

<u>C E R T I F I C A T E</u>

This is to certify that the attached proceedings in the matter of:

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A PUBLIC WORKSHOP

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Hyattsville, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Tobacco Products.

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ED SCHWEITZER

Official Reporter

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556